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&lt;210&gt; 280

&lt;211&gt; 874

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 280

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&lt;210&gt; 281

&lt;211&gt; 730

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 281

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&lt;210&gt; 282

&lt;211&gt; 699

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 282

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&lt;210&gt; 283

&lt;211&gt; 759

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 283

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&lt;210&gt; 284

&lt;211&gt; 764

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 284

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&lt;210&gt; 285

&lt;211&gt; 586

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens



&lt;400&gt; 285

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&lt;210&gt; 286

&lt;211&gt; 666

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 286

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atttct						666

&lt;210&gt; 287

&lt;211&gt; 782

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 287

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aa						782

&lt;210&gt; 288

&lt;211&gt; 707

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 288

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&lt;210&gt; 289

&lt;211&gt; 673

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 289

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&lt;210&gt; 290

&lt;211&gt; 573

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 290

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&lt;210&gt; 291

&lt;211&gt; 819

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 291

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&lt;210&gt; 292

&lt;211&gt; 664

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 292

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&lt;210&gt; 293

&lt;211&gt; 719

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 293

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652

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<212> DNA

<213> Homo Sapiens

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<211> 697

<212> DNA

<213> Homo Sapiens

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<211> 510

<212> DNA

<213> Homo Sapiens

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&lt;210&gt; 303

&lt;211&gt; 635

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 303

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&lt;210&gt; 304

&lt;211&gt; 847

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 304

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&lt;211&gt; 767

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 305

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&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 306

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&lt;211&gt; 831

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 307

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&lt;211&gt; 833

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&lt;213&gt; Homo Sapiens

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&lt;213&gt; Homo Sapiens

&lt;400&gt; 309

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&lt;210&gt; 310

&lt;211&gt; 1030

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 310

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ggggttaacc						1030

&lt;210&gt; 311

&lt;211&gt; 546

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 311

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gctaaaaata	aaagcacaga	aggaaaaaat	aattgatttg	tacataagct	aaattataat	180
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tgaggacct	gcaaaatgta	tactcgggtt	gtttttcttt	ttaaaaatat	tgtnaaacag	360
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cgggcc						546

&lt;210&gt; 312

&lt;211&gt; 518

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 312

aaaattatta	ntntaaaagg	ggaaaataggt	nggattnccn	tnttnagggc	aataattntg	60
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ttggcaacta	aggctcattt	ttccaaagggt	gttnctnang	tcnnctccct	ntnaaatcnt	240
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ctnctgctgc	tgttgctgct	gggcantnca	agggaaaacc	cccccgacaa	actgggataa	360
ngtgacctgn	ttgcncacnt	ctnngggccct	attnccttac	ctgncctgna	aatncttccc	420
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aacctccnac	ctttgggttan	cggggggtccc	ctncccc			518

&lt;210&gt; 313

&lt;211&gt; 660

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 313

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&lt;210&gt; 314

&lt;211&gt; 516

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 314

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caactcaata	ctgcttttagt	tcattttaaat	tttctttccc	aaaaatacac	tcctaaatat	480
acaaactata	caatcttatt	attttaatgc	tggtttt			516

&lt;210&gt; 315

&lt;211&gt; 677

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 315

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aaatttggtc	tcaaaaacaaa	tatactcatt	tcaaagaact	tccaactctt	ctccactgtg	180
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ttttacaaga cntcctt 677

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&lt;210&gt; 316

&lt;211&gt; 843

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 316

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gtcttaatac aaaggtaggt tatgaaaatg tatattaatt tgagatatag aaaagttttc 180
aaataataat gttttcaggg ttatatgcaa atagacacta aataagacaa ggtttctgca 240
aacatgatgt aacaataatg actggaactc tgaatgtgag aaattcagaa aatgaaccag 300
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caagaacctc ttgctgaatt ttcataataa actatttctt gttggcagtt tctaccccc 840
gga 843

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&lt;210&gt; 317

&lt;211&gt; 835

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 317

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gagaacgaga aaggagggag aaggagaggg aacgagaaag agaacgggag aaggagaagg 240
agagagaacg agagaagcag aagctaaaag agtcagaaaa agagagagat tctgctaagg 300
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&lt;210&gt; 318

&lt;211&gt; 582

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 318

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&lt;210&gt; 319

&lt;211&gt; 827

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 319

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&lt;210&gt; 320

&lt;211&gt; 598

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 320

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&lt;210&gt; 321

&lt;211&gt; 808

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 321

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cggacaagg	agccaatctt	gggaaaaa				808

&lt;210&gt; 322

&lt;211&gt; 629

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 322

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&lt;210&gt; 323

&lt;211&gt; 798

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 323

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ggagccaagg agaaaagg

798

&lt;210&gt; 324

&lt;211&gt; 754

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 324

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&lt;210&gt; 325

&lt;211&gt; 854

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 325

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&lt;210&gt; 326

&lt;211&gt; 760

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 326

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&lt;210&gt; 327

&lt;211&gt; 852

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 327

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&lt;210&gt; 328

&lt;211&gt; 799

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 328

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&lt;210&gt; 329

&lt;211&gt; 978

&lt;212&gt; DNA



&lt;213&gt; Homo Sapiens

&lt;400&gt; 329

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&lt;211&gt; 1017

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 330

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&lt;210&gt; 331

&lt;211&gt; 799

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 331

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&lt;211&gt; 881

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 332

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&lt;210&gt; 333

&lt;211&gt; 810

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 333

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<400> 336

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&lt;210&gt; 337

&lt;211&gt; 643

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 337

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&lt;210&gt; 338

&lt;211&gt; 831

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 338

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&lt;211&gt; 758

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 339

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&lt;211&gt; 840

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 340

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&lt;210&gt; 341

&lt;211&gt; 793

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 341

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&lt;210&gt; 342

&lt;211&gt; 906

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 342

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&lt;210&gt; 343

&lt;211&gt; 875

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 343

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&lt;210&gt; 344

&lt;211&gt; 629

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 344

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&lt;210&gt; 345

&lt;211&gt; 724

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 345

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&lt;210&gt; 346

&lt;211&gt; 907

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 346

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&lt;210&gt; 347

&lt;211&gt; 711

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 347

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&lt;211&gt; 862

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 348

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&lt;210&gt; 349

&lt;211&gt; 832

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 349

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&lt;210&gt; 353

&lt;211&gt; 875

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 353

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&lt;210&gt; 354

&lt;211&gt; 705

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 354

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&lt;210&gt; 355

&lt;211&gt; 862

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 355

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&lt;210&gt; 356

&lt;211&gt; 750

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 356

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&lt;210&gt; 357

&lt;211&gt; 725

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 357

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 ccgatcggaa aaccttcaag aggaggaaga agaaga 756

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&lt;210&gt; 361

&lt;211&gt; 726

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 361

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&lt;210&gt; 362

&lt;211&gt; 747

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 362

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&lt;210&gt; 363

&lt;211&gt; 1227

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 363

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&lt;210&gt; 364

&lt;211&gt; 831

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 364

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&lt;210&gt; 365

&lt;211&gt; 785

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 365

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&lt;210&gt; 366

&lt;211&gt; 816

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 366

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&lt;210&gt; 367

&lt;211&gt; 803

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 367

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&lt;210&gt; 368

&lt;211&gt; 809

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 368

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&lt;210&gt; 369

&lt;211&gt; 826

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 369

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&lt;210&gt; 370

&lt;211&gt; 783

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 370

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gagctttgag	aaacaatgct	tttgccccaa	tgaccctctg	gttcccttaa	ctacagatct	540
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tgc						783



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 <212> DNA  
 <213> Homo Sapiens

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 cggaggacag cctcctggcc gccgaagagg ccgccgccaa ggctgaagcc gacgtagctt 180  
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 aactgaaaga ggcaaagcac attgctgaag atgccgaccg caaatatgaa gaggtggccc 420

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gtgaaaaact tc                                     792

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&lt;210&gt; 374

&lt;211&gt; 745

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 374

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gaaaaataa aaggaggatt ccaaa                                     745

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&lt;210&gt; 375

&lt;211&gt; 734

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 375

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atactggaaa cttg                                     734

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&lt;210&gt; 376

&lt;211&gt; 822

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 376

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&lt;210&gt; 377

&lt;211&gt; 812

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 377

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&lt;210&gt; 378

&lt;211&gt; 870

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 378

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870

&lt;210&gt; 379

&lt;211&gt; 837

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 379

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&lt;210&gt; 380

&lt;211&gt; 793

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 380

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&lt;210&gt; 381

&lt;211&gt; 807

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 381

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&lt;211&gt; 800

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 382

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&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 383

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&lt;211&gt; 2651

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 384

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&lt;211&gt; 753

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 388

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&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

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&lt;213&gt; Homo Sapiens

&lt;400&gt; 390



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&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 391

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&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 392

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&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 393

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&lt;210&gt; 394

&lt;211&gt; 813

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 394

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&lt;210&gt; 395

&lt;211&gt; 762

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 395

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&lt;211&gt; 822

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 396

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&lt;211&gt; 812

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 397

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&lt;211&gt; 751

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 398

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&lt;213&gt; Homo Sapiens

&lt;400&gt; 399

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&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

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&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

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&lt;213&gt; Homo Sapiens

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&lt;211&gt; 758

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&lt;213&gt; Homo Sapiens

&lt;400&gt; 406

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&lt;210&gt; 407

&lt;211&gt; 778

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 407

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&lt;210&gt; 408

&lt;211&gt; 752

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 408

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&lt;210&gt; 409

&lt;211&gt; 736

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 409

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&lt;210&gt; 410

&lt;211&gt; 766

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 410

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&lt;210&gt; 411

&lt;211&gt; 812

&lt;212&gt; DNA



&lt;213&gt; Homo Sapiens

&lt;400&gt; 411

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&lt;210&gt; 412

&lt;211&gt; 857

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 412

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&lt;210&gt; 413

&lt;211&gt; 790

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 413

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 <212> DNA  
 <213> Homo Sapiens

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 <212> DNA  
 <213> Homo Sapiens

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<210> 416  
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 <212> DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 416

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&lt;210&gt; 417

&lt;211&gt; 880

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 417

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&lt;210&gt; 418

&lt;211&gt; 763

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 418

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&lt;210&gt; 419

&lt;211&gt; 753

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 419

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&lt;210&gt; 420

&lt;211&gt; 799

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 420

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&lt;210&gt; 421

&lt;211&gt; 770

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 421

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&lt;210&gt; 422

&lt;211&gt; 733

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 422

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&lt;210&gt; 423

&lt;211&gt; 862

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 423

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&lt;210&gt; 424

&lt;211&gt; 859

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 424

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&lt;210&gt; 425

&lt;211&gt; 837

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 425

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&lt;210&gt; 426

&lt;211&gt; 724

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 426

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catc						724

&lt;210&gt; 427

&lt;211&gt; 981

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 427

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&lt;210&gt; 428

&lt;211&gt; 655

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 428

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&lt;210&gt; 429

&lt;211&gt; 788

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 429

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tcccagca						788

&lt;210&gt; 430

&lt;211&gt; 655

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 430

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&lt;210&gt; 431

&lt;211&gt; 844

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 431

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gaaa						844

&lt;210&gt; 432



&lt;211&gt; 807

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 432

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&lt;210&gt; 433

&lt;211&gt; 866

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 433

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&lt;210&gt; 434

&lt;211&gt; 764

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 434

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 <212> DNA  
 <213> Homo Sapiens

<400> 437

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&lt;210&gt; 438

&lt;211&gt; 678

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 438

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&lt;210&gt; 439

&lt;211&gt; 826

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 439

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 <212> DNA  
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 aattttctga agcaagctga gaggcaggca gaaagatttg atgccaaaaa aaaaaaaatc 240  
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 gaagcctact ggtacttgaa ggtaagaaca gtatgaccag ggagtttctg gtggacttcc 780  
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 <212> DNA  
 <213> Homo Sapiens

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 <212> DNA  
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 <212> DNA  
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<210> 445  
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 <212> DNA  
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cct						783

&lt;210&gt; 446

&lt;211&gt; 866

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 446

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&lt;210&gt; 447

&lt;211&gt; 789

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 447

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789

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 <213> Homo Sapiens

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<210> 449  
 <211> 936  
 <212> DNA  
 <213> Homo Sapiens

&lt;400&gt; 449

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 <213> Homo Sapiens

&lt;400&gt; 450

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&lt;210&gt; 451

&lt;211&gt; 909

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 451

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&lt;210&gt; 452

&lt;211&gt; 672

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 452

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&lt;210&gt; 453



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 <212> DNA  
 <213> Homo Sapiens

<400> 453

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 <211> 703  
 <212> DNA  
 <213> Homo Sapiens

<400> 454

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 <212> DNA  
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<400> 455

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&lt;210&gt; 456

&lt;211&gt; 740

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 456

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ccacacacac accacattct tctacccn taagagaagg taggttcctt tcacaataag	720
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&lt;210&gt; 457

&lt;211&gt; 726

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 457

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&lt;210&gt; 458

&lt;211&gt; 870

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 458

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&lt;210&gt; 459

&lt;211&gt; 761

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 459

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&lt;210&gt; 460

&lt;211&gt; 876

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 460

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 <213> Homo Sapiens

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 <212> DNA  
 <213> Homo Sapiens

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<210> 463  
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 <212> DNA  
 <213> Homo Sapiens

<400> 463  
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aaac						784

&lt;210&gt; 464

&lt;211&gt; 850

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 464

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ctggaaggcc						850

&lt;210&gt; 465

&lt;211&gt; 759

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 465

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&lt;210&gt; 466

&lt;211&gt; 1240

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 466

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&lt;210&gt; 467

&lt;211&gt; 885

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 467

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&lt;210&gt; 468

&lt;211&gt; 748

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 468

gcaaatcaga	gaaataacca	cattagaaaa	agcaatatgc	cttttttttt	aaaatggcac	60
atcaagtgc	tctcatttta	aaatatctct	tttcttaacc	cttaatttga	atgcaaaatg	120
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&lt;210&gt; 469

&lt;211&gt; 770

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 469

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agctgagttt	gcgggaaagg	atgtntttcca	cgccgcttnt	cgcanaacact	ggcactgnct	660
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&lt;210&gt; 470

&lt;211&gt; 892

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 470

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&lt;210&gt; 471

&lt;211&gt; 759

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 471

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&lt;210&gt; 472

&lt;211&gt; 852

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 472

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&lt;210&gt; 473

&lt;211&gt; 804

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 473

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804

&lt;210&gt; 474

&lt;211&gt; 819

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 474

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&lt;210&gt; 475

&lt;211&gt; 721

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 475

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a						721

&lt;210&gt; 476

&lt;211&gt; 442

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 476

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angcacacca	cangctcagn	ccatgttntn	agcccatcag	nttcagttna	catngccaca	240
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<212> DNA  
<213> Homo Sapiens

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<212> DNA  
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&lt;210&gt; 480

&lt;211&gt; 812

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 480

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&lt;210&gt; 481

&lt;211&gt; 1127

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 481

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<211> 773

<212> DNA

<213> Homo Sapiens

<400> 482

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<210> 483

<211> 794

<212> DNA

<213> Homo Sapiens

<400> 483

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<210> 484

<211> 788

<212> DNA

<213> Homo Sapiens

<400> 484

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&lt;210&gt; 485

&lt;211&gt; 430

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 485

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&lt;210&gt; 486

&lt;211&gt; 831

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 486

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&lt;210&gt; 487

&lt;211&gt; 728

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 487

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&lt;210&gt; 488

&lt;211&gt; 788

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 488

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&lt;210&gt; 489

&lt;211&gt; 875

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 489

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&lt;210&gt; 490

&lt;211&gt; 844

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 490

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&lt;210&gt; 491

&lt;211&gt; 825

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 491

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&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

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&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 493

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&lt;213&gt; Homo Sapiens

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&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 495

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&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 496

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&lt;211&gt; 787

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 500

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&lt;213&gt; Homo Sapiens

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&lt;211&gt; 884

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

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&lt;211&gt; 612

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 504

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&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

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&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 506

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&lt;211&gt; 735

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 507

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&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 508

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&lt;211&gt; 818

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 509

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&lt;213&gt; Homo Sapiens

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&lt;211&gt; 926

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 518

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&lt;210&gt; 519

&lt;211&gt; 789

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 519

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&lt;211&gt; 827

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

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&lt;213&gt; Homo Sapiens

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&lt;211&gt; 766

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 524

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&lt;211&gt; 847

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 525

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&lt;213&gt; Homo Sapiens

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&lt;213&gt; Homo Sapiens

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&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

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&lt;211&gt; 802

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

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&lt;211&gt; 901

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

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&lt;210&gt; 537

&lt;211&gt; 761

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 537

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&lt;210&gt; 538

&lt;211&gt; 869

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 538

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&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 546

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ggccactgtg cccacccaag ccctggggcg taccaatcc tccctgctg cccctggggg     1440
catgaagaac cccccagacc aaccgctcaa gcacctctc accacaagtg tggctctacga     1500
cacgttcatg ctaaagcacc agtgcatgtg cgggaacaca cagtgccacc ctgagcatgc     1560
tgcccgatc cagagcatct ggtcccggt gcaggagaca ggctgctta gcaagtgcga     1620
gcggatccga ggtcgcaaaag ccacgctaga tgagatctga acagtgcact ctgaatacca     1680

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caccctgctc tatgggacca gtccctcctcaa ccggcagaag ctagacagca agaagttgct 1740
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aattt

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&lt;210&gt; 547

&lt;211&gt; 897

&lt;212&gt; PRT

&lt;213&gt; Homo Sapiens

&lt;400&gt; 547

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Glu Phe Leu Leu Ser Lys Ser Lys Glu Pro Thr Pro Gly Gly Leu Asn
 1             5             10             15
His Ser Leu Pro Gln His Pro Lys Cys Trp Gly Ala His His Ala Ser
      20             25             30
Leu Asp Gln Ser Ser Pro Pro Gln Ser Gly Pro Pro Gly Thr Pro Pro
      35             40             45
Ser Tyr Lys Leu Pro Leu Pro Gly Pro Tyr Asp Ser Arg Asp Asp Phe
      50             55             60
Pro Leu Arg Lys Thr Ala Ser Glu Pro Asn Leu Lys Val Arg Ser Arg
      65             70             75             80
Leu Lys Gln Lys Val Ala Glu Arg Arg Ser Ser Pro Leu Leu Arg Arg
      85             90             95
Lys Asp Gly Thr Val Ile Ser Thr Phe Lys Lys Arg Ala Val Glu Ile
      100             105             110
Thr Gly Ala Gly Pro Gly Ala Ser Ser Val Cys Asn Ser Ala Pro Gly
      115             120             125
Ser Gly Pro Ser Ser Pro Asn Ser Ser His Ser Thr Ile Ala Glu Asn
      130             135             140
Gly Phe Thr Gly Ser Val Pro Asn Ile Pro Thr Glu Met Leu Pro Gln
      145             150             155             160
His Arg Ala Leu Pro Leu Asp Ser Ser Pro Asn Gln Phe Ser Leu Tyr
      165             170             175
Thr Ser Pro Ser Leu Pro Asn Ile Ser Leu Gly Leu Gln Ala Thr Val
      180             185             190
Thr Val Thr Asn Ser His Leu Thr Ala Ser Pro Lys Leu Ser Thr Gln
      195             200             205
Gln Glu Ala Glu Arg Gln Ala Leu Gln Ser Leu Arg Gln Gly Gly Thr

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210	215	220
Leu Thr Gly Lys Phe Met Ser Thr Ser Ser Ile Pro Gly Cys Leu Leu		
225	230	235
Gly Val Ala Leu Glu Gly Asp Gly Ser Pro His Gly His Ala Ser Leu		240
	245	250
Leu Gln His Val Leu Leu Leu Glu Gln Ala Arg Gln Gln Ser Thr Leu		255
	260	265
Ile Ala Val Pro Leu His Gly Gln Ser Pro Leu Val Thr Gly Glu Arg		270
	275	280
Val Ala Thr Ser Met Arg Thr Val Gly Lys Leu Pro Arg His Arg Pro		285
	290	295
Leu Ser Arg Thr Gln Ser Ser Pro Leu Pro Gln Ser Pro Gln Ala Leu		300
305	310	315
Gln Gln Leu Val Met Gln Gln Gln His Gln Gln Phe Leu Glu Lys Gln		320
	325	330
Lys Gln Gln Gln Leu Gln Leu Gly Lys Ile Leu Thr Lys Thr Gly Glu		335
	340	345
Leu Pro Arg Gln Pro Thr Thr His Pro Glu Glu Thr Glu Glu Glu Leu		350
	355	360
Thr Glu Gln Gln Glu Val Leu Leu Gly Glu Gly Ala Leu Thr Met Pro		365
	370	375
Arg Glu Gly Ser Thr Glu Ser Glu Ser Thr Gln Glu Asp Leu Glu Glu		380
385	390	395
Glu Asp Glu Glu Glu Asp Gly Glu Glu Glu Asp Cys Ile Gln Val		400
	405	410
Lys Asp Glu Glu Gly Glu Ser Gly Ala Glu Glu Gly Pro Asp Leu Glu		415
	420	425
Glu Pro Gly Ala Gly Tyr Lys Lys Leu Phe Ser Asp Ala Gln Pro Leu		430
	435	440
Gln Pro Leu Gln Val Tyr Gln Ala Pro Leu Ser Leu Ala Thr Val Pro		445
	450	455
His Gln Ala Leu Gly Arg Thr Gln Ser Ser Pro Ala Ala Pro Gly Gly		460
465	470	475
Met Lys Asn Pro Pro Asp Gln Pro Val Lys His Leu Phe Thr Thr Ser		480
	485	490
Val Val Tyr Asp Thr Phe Met Leu Lys His Gln Cys Met Cys Gly Asn		495
	500	505
Thr His Val His Pro Glu His Ala Gly Arg Ile Gln Ser Ile Trp Ser		510
	515	520
Arg Leu Gln Glu Thr Gly Leu Leu Ser Lys Cys Glu Arg Ile Arg Gly		525
	530	535
Arg Lys Ala Thr Leu Asp Glu Ile Gln Thr Val His Ser Glu Tyr His		540
545	550	555
Thr Leu Leu Tyr Gly Thr Ser Pro Leu Asn Arg Gln Lys Leu Asp Ser		560
	565	570
Lys Lys Leu Leu Gly Pro Ile Ser Gln Lys Met Tyr Ala Val Leu Pro		575
	580	585
Cys Gly Gly Ile Gly Val Asp Ser Asp Thr Val Trp Asn Glu Met His		590
	595	600
Ser Ser Ser Ala Val Arg Met Ala Val Gly Cys Leu Leu Glu Leu Ala		605
	610	615
Phe Lys Val Ala Ala Gly Glu Leu Lys Asn Gly Phe Ala Ile Ile Arg		620
625	630	635
Pro Pro Gly His His Ala Glu Glu Ser Thr Ala Met Gly Phe Cys Phe		640
	645	650
		655

Phe Asn Ser Val Ala Ile Thr Ala Lys Leu Leu Gln Gln Lys Leu Asn  
 660 665 670  
 Val Gly Lys Val Leu Ile Val Asp Trp Asp Ile His His Gly Asn Gly  
 675 680 685  
 Thr Gln Gln Ala Phe Tyr Asn Asp Pro Ser Val Leu Tyr Ile Ser Leu  
 690 695 700  
 His Arg Tyr Asp Asn Gly Asn Phe Phe Pro Gly Ser Gly Ala Pro Glu  
 705 710 715 720  
 Glu Val Gly Gly Gly Pro Gly Val Gly Tyr Asn Val Asn Val Ala Trp  
 725 730 735  
 Thr Gly Gly Val Asp Pro Pro Ile Gly Asp Val Glu Tyr Leu Thr Ala  
 740 745 750  
 Phe Arg Thr Val Val Met Pro Ile Ala His Glu Phe Ser Pro Asp Val  
 755 760 765  
 Val Leu Val Ser Ala Gly Phe Asp Ala Val Glu Gly His Leu Ser Pro  
 770 775 780  
 Leu Gly Gly Tyr Ser Val Thr Ala Arg Cys Phe Gly His Leu Thr Arg  
 785 790 795 800  
 Gln Leu Met Thr Leu Ala Gly Gly Arg Val Val Leu Ala Leu Glu Gly  
 805 810 815  
 Gly His Asp Leu Thr Ala Ile Cys Asp Ala Ser Glu Ala Cys Val Ser  
 820 825 830  
 Ala Leu Leu Ser Val Lys Leu Gln Pro Leu Asp Glu Ala Val Leu Gln  
 835 840 845  
 Gln Lys Pro Asn Ile Asn Ala Val Ala Thr Leu Glu Lys Val Ile Glu  
 850 855 860  
 Ile Gln Ser Lys His Trp Ser Cys Val Gln Lys Phe Ala Ala Gly Leu  
 865 870 875 880  
 Gly Arg Ser Leu Arg Gly Ala Gln Ala Gly Glu Thr Glu Glu Ala Glu  
 885 890 895  
 Met

<210> 548  
 <211> 1298  
 <212> DNA  
 <213> Homo Sapiens

<400> 548  
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 tgatggagag agaaagcatc naaagcttct ggaagcaatc agttcccttg atggaaagaa 180  
 taggcggaaa ttggctgana ggtctgaggc tagtctgaag gtgtcagagt tcaatgtcag 240  
 ttctgaagga tcaggagaaa agctggctct tgcagatctg cttgagcctg ttaaaaacttc 300  
 atcttctttg gccactgtga aaaagcaact gagtagagtc anatcaaaga anacagtgga 360  
 gttacctctg aacaaagaag agattgaacg gatccacaga gaatagcatt caataaaaacg 420  
 cacaagtctt ctccaaatgg gacctgtcg tctgaagaa ccggcaggca gagcagctgg 480  
 tttttccctt ggagaaagag gagccagcca ttgctcccat tgaacatgtg ctgagtggt 540  
 ggaaggcaag aactcccttg gagcaggaaa ttttcaacct cctccataag aacaagcagc 600  
 cagtgcacaga ccctttactg accctgtgg aaaaggcctc tctccgagcc atgagcctag 660  
 aagaggcaaa gatgcgacga gcagagcttc agagggctcg ggctctgcag tctactatg 720  
 angccaaggc tcgaagagag aagaaaatcn aaagttaaaa gtatcacaaa gtcgtgaaga 780  
 aaggaaaggc caagaaagcc ctaaaagagt ttgagcagct gcggaagggt aatccagctg 840  
 ccgactaga agaacgaaga aaagaggaaa gaaggaggag gagaagaag aagaacaagg 900  
 agaagaagaa agaagaaggg agaaggagaa gaaaagaagg agaagaggaa aaggaagaag 960



gagaaagaaa aggagaagga aaaggaaaag aaggagaaga aagaagaact aagaagaagg 1020  
 agaggaagaa taagaaggaa agaagaaaga aaaaagtnaa agaagaagaa agaaggaaga 1080  
 aggaaagaag aggaagaact nagaagaaga aagaggagga aagaagaaag aagaataagg 1140  
 aacnagaaag aaggagaaga aagaataaga agaggaagaa gaaaaagaag aaaagaagaa 1200  
 ggaaagaagg agaaaaagga agaaaaaagg aagaagaaag tagaaagcgg aagaagaaa 1260  
 agaaagtata agaaggaaga agaagaaaga aggaaaaa 1298

&lt;210&gt; 549

&lt;211&gt; 236

&lt;212&gt; PRT

&lt;213&gt; Homo Sapiens

&lt;400&gt; 549

Ala Ala Glu Met Thr Ala Asn Arg Leu Ala Glu Ser Leu Leu Ala Leu  
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 Ser Gln Glu Glu Leu Ala Asp Leu Pro Lys Asp Tyr Leu Leu Ser Glu  
 20 25 30  
 Ser Glu Asp Glu Gly Asp Asn Asp Gly Glu Arg Lys His Lys Leu Leu  
 35 40 45  
 Glu Ala Ile Ser Ser Leu Asp Gly Lys Asn Arg Arg Lys Leu Ala Arg  
 50 55 60  
 Ser Glu Ala Ser Leu Lys Val Ser Glu Phe Asn Val Ser Ser Glu Gly  
 65 70 75 80  
 Ser Gly Glu Lys Leu Val Leu Ala Asp Leu Leu Glu Pro Val Lys Thr  
 85 90 95  
 Ser Ser Ser Leu Ala Thr Val Lys Lys Gln Leu Ser Arg Val Ser Lys  
 100 105 110  
 Thr Val Glu Leu Pro Leu Asn Lys Glu Glu Ile Glu Arg Ile His Arg  
 115 120 125  
 Glu Ile Ala Phe Asn Lys Thr His Lys Ser Ser Pro Asn Gly Thr Leu  
 130 135 140  
 Ser Ser Val Leu Lys Asn Arg Gln Ala Glu Gln Leu Val Phe Pro Leu  
 145 150 155 160  
 Glu Lys Glu Glu Pro Ala Ile Ala Pro Ile Glu His Val Leu Ser Gly  
 165 170 175  
 Trp Lys Ala Arg Thr Pro Leu Glu Gln Glu Ile Phe Asn Leu Leu His  
 180 185 190  
 Lys Asn Lys Gln Pro Val Thr Asp Pro Leu Leu Thr Pro Val Glu Lys  
 195 200 205  
 Ala Ser Leu Arg Ala Met Ser Leu Glu Glu Ala Lys Met Arg Arg Ala  
 210 215 220  
 Glu Leu Gln Arg Ala Arg Ala Leu Gln Ser Tyr Tyr  
 225 230 235

&lt;210&gt; 550

&lt;211&gt; 2236

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 550

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 ttccggcata aggtggattt tctgattgaa aatgatgcag agaaggacta tctctatgat 180  
 gtgctgcgaa tgtaccacca gaccatggac gtggccgtgc tctgtggaga cctgaagctg 240  
 gtcacatgat aaccagccg tctgectctg tttgatgcc a ttcggccgct gatccactg 300

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ttccagctta aaaaaa 2236

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&lt;210&gt; 551

&lt;211&gt; 652

&lt;212&gt; PRT

&lt;213&gt; Homo Sapiens

&lt;400&gt; 551

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Met Asp Arg Lys Val Ala Arg Glu Phe Arg His Lys Val Asp Phe Leu
1           5           10           15
Ile Glu Asn Asp Ala Glu Lys Asp Tyr Leu Tyr Asp Val Leu Arg Met
20           25           30
Tyr His Gln Thr Met Asp Val Ala Val Leu Val Gly Asp Leu Lys Leu
35           40           45
Val Ile Asn Glu Pro Ser Arg Leu Pro Leu Phe Asp Ala Ile Arg Pro
50           55           60
Leu Ile Pro Leu Lys His Gln Val Glu Tyr Asp Gln Leu Thr Pro Arg
65           70           75           80
Arg Ser Arg Lys Leu Lys Glu Val Arg Leu Asp Arg Leu His Pro Glu
85           90           95
Gly Leu Gly Leu Ser Val Arg Gly Gly Leu Glu Phe Gly Cys Gly Leu
100          105          110
Phe Ile Ser His Leu Ile Lys Gly Gly Gln Ala Asp Ser Val Gly Leu

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115					120					125					
Gln	Val	Gly	Asp	Glu	Ile	Val	Arg	Ile	Asn	Gly	Tyr	Ser	Ile	Ser	Ser
130					135					140					
Cys	Thr	His	Glu	Glu	Val	Ile	Asn	Leu	Ile	Arg	Thr	Lys	Lys	Thr	Val
145	150					155					160				
Ser	Ile	Lys	Val	Arg	His	Ile	Gly	Leu	Ile	Pro	Val	Lys	Ser	Ser	Pro
165					170					175					
Asp	Glu	Pro	Leu	Thr	Trp	Gln	Tyr	Val	Asp	Gln	Phe	Val	Ser	Glu	Ser
180					185					190					
Gly	Gly	Val	Arg	Gly	Ser	Leu	Gly	Ser	Pro	Gly	Asn	Arg	Glu	Asn	Lys
195					200					205					
Glu	Lys	Lys	Val	Phe	Ile	Ser	Leu	Val	Gly	Ser	Arg	Gly	Leu	Gly	Cys
210					215					220					
Ser	Ile	Ser	Ser	Gly	Pro	Ile	Gln	Lys	Pro	Gly	Ile	Phe	Ile	Ser	His
225	230					235					240				
Val	Lys	Pro	Gly	Ser	Leu	Ser	Ala	Glu	Val	Gly	Leu	Glu	Ile	Gly	Asp
245					250					255					
Gln	Ile	Val	Glu	Val	Asn	Gly	Val	Asp	Phe	Ser	Asn	Leu	Asp	His	Lys
260					265					270					
Glu	Ala	Val	Asn	Val	Leu	Lys	Asn	Ser	Arg	Ser	Leu	Thr	Ile	Ser	Ile
275					280					285					
Val	Ala	Ala	Ala	Gly	Arg	Glu	Leu	Phe	Met	Thr	Asp	Arg	Glu	Arg	Leu
290					295					300					
Ala	Glu	Ala	Arg	Gln	Arg	Glu	Leu	Gln	Arg	Gln	Glu	Leu	Leu	Met	Gln
305	310					315					320				
Lys	Arg	Leu	Ala	Met	Glu	Ser	Asn	Lys	Ile	Leu	Gln	Glu	Gln	Gln	Glu
325					330					335					
Met	Glu	Arg	Gln	Arg	Arg	Lys	Glu	Ile	Ala	Gln	Lys	Ala	Ala	Glu	Glu
340					345					350					
Asn	Glu	Arg	Tyr	Arg	Lys	Glu	Met	Glu	Gln	Ile	Val	Glu	Glu	Glu	Glu
355					360					365					
Lys	Phe	Lys	Lys	Gln	Trp	Glu	Glu	Asp	Trp	Gly	Ser	Lys	Glu	Gln	Leu
370					375					380					
Leu	Leu	Pro	Lys	Thr	Ile	Thr	Ala	Glu	Val	His	Pro	Val	Pro	Leu	Arg
385	390					395					400				
Lys	Pro	Lys	Tyr	Asp	Gln	Gly	Val	Glu	Pro	Glu	Leu	Glu	Pro	Ala	Asp
405					410					415					
Asp	Leu	Asp	Gly	Thr	Glu	Glu	Gln	Gly	Glu	Gln	Asp	Phe	Arg	Lys	
420					425					430					
Tyr	Glu	Glu	Gly	Phe	Asp	Pro	Tyr	Ser	Met	Phe	Thr	Pro	Glu	Gln	Ile
435					440					445					
Met	Gly	Lys	Asp	Val	Arg	Leu	Leu	Arg	Ile	Lys	Lys	Glu	Gly	Ser	Leu
450					455					460					
Asp	Leu	Ala	Leu	Glu	Gly	Gly	Val	Asp	Ser	Pro	Ile	Gly	Lys	Val	Val
465	470					475					480				
Val	Ser	Ala	Val	Tyr	Glu	Arg	Gly	Ala	Ala	Glu	Arg	His	Gly	Gly	Ile
485					490					495					
Val	Lys	Gly	Asp	Glu	Ile	Met	Ala	Ile	Asn	Gly	Lys	Ile	Val	Thr	Asp
500					505					510					
Tyr	Thr	Leu	Ala	Glu	Ala	Asp	Ala	Ala	Leu	Gln	Lys	Ala	Trp	Asn	Gln
515					520					525					
Gly	Gly	Asp	Trp	Ile	Asp	Leu	Val	Val	Ala	Val	Cys	Pro	Pro	Lys	Glu
530	535					540					545				
Tyr	Asp	Asp	Glu	Leu	Thr	Phe	Leu	Leu	Lys	Ser	Lys	Arg	Gly	Asn	Gln
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<211> 2162
<212> DNA
<213> Homo Sapiens
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-286-

aa

2162

<210> 553  
 <211> 403  
 <212> PRT  
 <213> Homo Sapiens

<400> 553  
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 20 25 30  
 Tyr His Gln Thr Met Asp Val Ala Val Leu Val Gly Asp Leu Lys Leu  
 35 40 45  
 Val Ile Asn Glu Pro Ser Arg Leu Pro Leu Phe Asp Ala Ile Arg Pro  
 50 55 60  
 Leu Ile Pro Leu Lys His Gln Val Glu Tyr Asp Gln Leu Thr Pro Arg  
 65 70 75 80  
 Arg Ser Arg Lys Leu Lys Glu Val Arg Leu Asp Arg Leu His Pro Glu  
 85 90 95  
 Gly Leu Gly Leu Ser Val Arg Gly Gly Leu Glu Phe Gly Cys Gly Leu  
 100 105 110  
 Phe Ile Ser His Leu Ile Lys Gly Gly Gln Ala Asp Ser Val Gly Leu  
 115 120 125  
 Gln Val Gly Asp Glu Ile Val Arg Ile Asn Gly Tyr Ser Ile Ser Ser  
 130 135 140  
 Cys Thr His Glu Glu Val Ile Asn Leu Ile Arg Thr Lys Lys Thr Val  
 145 150 155 160  
 Ser Ile Lys Val Arg His Ile Gly Leu Ile Pro Val Lys Ser Ser Pro  
 165 170 175  
 Asp Glu Pro Leu Thr Trp Gln Tyr Val Asp Gln Phe Val Ser Glu Ser  
 180 185 190  
 Gly Gly Val Arg Gly Ser Leu Gly Ser Pro Gly Asn Arg Glu Asn Lys  
 195 200 205  
 Glu Lys Lys Val Phe Ile Ser Leu Val Gly Ser Arg Gly Leu Gly Cys  
 210 215 220  
 Ser Ile Ser Ser Gly Pro Ile Gln Lys Pro Gly Ile Phe Ile Ser His  
 225 230 235 240  
 Val Lys Pro Gly Ser Leu Ser Ala Glu Val Gly Leu Glu Ile Gly Asp  
 245 250 255  
 Gln Ile Val Glu Val Asn Gly Val Asp Phe Ser Asn Leu Asp His Lys  
 260 265 270  
 Glu Ala Val Asn Val Leu Lys Asn Ser Arg Ser Leu Thr Ile Ser Ile  
 275 280 285  
 Val Ala Ala Ala Gly Arg Glu Leu Phe Met Thr Asp Arg Glu Arg Leu  
 290 295 300  
 Ala Glu Ala Arg Gln Arg Glu Leu Gln Arg Gln Glu Leu Leu Met Gln  
 305 310 315 320  
 Lys Arg Leu Ala Met Glu Ser Asn Lys Ile Leu Gln Glu Gln Gln Glu  
 325 330 335  
 Met Glu Arg Gln Arg Arg Lys Glu Ile Ala Gln Lys Ala Ala Glu Glu  
 340 345 350  
 Asn Glu Arg Tyr Arg Lys Glu Met Glu Gln Ile Val Glu Glu Glu Glu  
 355 360 365  
 Lys Phe Lys Lys Gln Trp Glu Glu Asp Trp Gly Ser Lys Glu Gln Leu

370                                      375                                      380  
 Leu Leu Pro Lys Thr Ile Thr Ala Glu Val His Pro Val Pro Leu Arg  
 385                                      390                                      395                                      400  
 Lys Pro Lys

<210> 554  
 <211> 1789  
 <212> DNA  
 <213> Homo Sapiens

<400> 554  
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<210> 555  
 <211> 493  
 <212> PRT  
 <213> Homo Sapiens

<400> 555  
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 Glu Ile Glu Glu Ser Gln Leu Lys Phe Leu Arg Asn Asp Leu Ala Glu  
 20                                      25                                      30  
 Tyr Gln Arg Thr Cys Glu Asp Leu Lys Glu Gln Leu Lys His Lys Glu  
 35                                      40                                      45

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Phe Leu Leu Ala Ala Asn Thr Cys Asn Arg Val Gly Gly Leu Cys Leu
 50                               55                               60
Lys Cys Ala Gln His Glu Ala Val Leu Ser Gln Thr His Thr Asn Val
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His Met Gln Thr Ile Glu Arg Leu Val Lys Glu Arg Asp Asp Leu Met
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Ser Ala Leu Val Ser Val Arg Ser Ser Leu Ala Asp Thr Gln Gln Arg
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Glu Ala Ser Ala Tyr Glu Gln Val Lys Gln Val Leu Gln Ile Ser Glu
                               115                               120                               125
Glu Ala Asn Phe Glu Lys Thr Lys Ala Leu Ile Gln Cys Asp Gln Leu
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Arg Lys Glu Leu Glu Arg Gln Ala Glu Arg Leu Glu Lys Glu Leu Ala
145                               150                               155                               160
Ser Gln Gln Glu Lys Arg Ala Ile Glu Lys Asp Met Met Lys Lys Glu
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Ile Thr Lys Glu Arg Glu Tyr Met Gly Ser Lys Met Leu Ile Leu Ser
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Gln Asn Ile Ala Gln Leu Glu Ala Gln Val Glu Lys Val Thr Lys Glu
195                               200                               205
Lys Ile Ser Ala Ile Asn Gln Leu Glu Glu Ile Gln Ser Gln Leu Ala
210                               215                               220
Ser Arg Glu Met Asp Val Thr Lys Val Cys Gly Glu Met Arg Tyr Gln
225                               230                               235                               240
Leu Asn Lys Thr Asn Met Glu Lys Asp Glu Ala Glu Lys Glu His Arg
                               245                               250                               255
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Ile Glu Lys Leu Arg Ile Glu Leu Asp Glu Ser Lys Gln His Leu Glu
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Gln Glu Gln Gln Lys Ala Ala Leu Ala Arg Glu Glu Cys Leu Arg Leu
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Thr Glu Leu Leu Gly Glu Ser Glu His Gln Leu His Leu Thr Arg Gln
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Glu Lys Asp Ser Ile Gln Gln Ser Phe Ser Lys Glu Ala Lys Ala Gln
                               325                               330                               335
Ala Leu Gln Ala Gln Gln Arg Glu Gln Glu Leu Thr Gln Lys Ile Gln
340                               345                               350
Gln Met Glu Ala Gln His Asp Lys Thr Glu Asn Glu Gln Tyr Leu Leu
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Leu Thr Ser Gln Asn Thr Phe Leu Thr Lys Leu Lys Glu Glu Cys Cys
370                               375                               380
Thr Leu Ala Lys Lys Leu Glu Gln Ile Ser Gln Lys Thr Arg Ser Glu
385                               390                               395                               400
Ile Ala Gln Leu Ser Gln Glu Lys Arg Tyr Thr Tyr Asp Lys Leu Gly
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Lys Leu Gln Arg Arg Asn Glu Glu Leu Glu Glu Gln Cys Val Gln His
420                               425                               430
Gly Arg Val His Glu Thr Met Lys Gln Arg Leu Arg Gln Leu Asp Lys
435                               440                               445
His Ser Gln Ala Thr Ala Gln Gln Leu Val Gln Leu Leu Ser Lys Gln
450                               455                               460
Asn Gln Leu Leu Leu Glu Arg Gln Ser Leu Ser Glu Glu Val Asp Arg
465                               470                               475                               480
Leu Arg Thr Gln Leu Pro Ser Met Pro Gln Ser Asp Cys

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485

490

<210> 556  
 <211> 1306  
 <212> DNA  
 <213> Homo Sapiens

&lt;400&gt; 556

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cggcaaagga gaaaagaaat tgcccagaag gcagcagagg aaaatgagag ataccggaag      240
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<210> 557  
 <211> 328  
 <212> PRT  
 <213> Homo Sapiens

&lt;400&gt; 557

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Arg Arg Lys Glu Ile Ala Gln Lys Ala Ala Glu Glu Asn Glu Arg Tyr
 20          25          30
Arg Lys Glu Met Glu Gln Ile Val Glu Glu Glu Glu Lys Phe Lys Lys
 35          40          45
Gln Trp Glu Glu Asp Trp Gly Ser Lys Glu Gln Leu Leu Leu Pro Lys
 50          55          60
Thr Ile Thr Ala Glu Val His Pro Val Pro Leu Arg Lys Pro Lys Tyr
 65          70          75          80
Asp Gln Gly Val Glu Pro Glu Leu Glu Pro Ala Asp Asp Leu Asp Gly
 85          90          95
Gly Thr Glu Glu Gln Gly Glu Gln Asp Phe Arg Lys Tyr Glu Glu Gly
100          105          110
Phe Asp Pro Tyr Ser Met Phe Thr Pro Glu Gln Ile Met Gly Lys Asp
115          120          125
Val Arg Leu Leu Arg Ile Lys Lys Glu Gly Ser Leu Asp Leu Ala Leu
130          135          140

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Glu Gly Gly Val Asp Ser Pro Ile Gly Lys Val Val Val Ser Ala Val  
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 Tyr Glu Arg Gly Ala Ala Glu Arg His Gly Gly Ile Val Lys Gly Asp  
 165 170 175  
 Glu Ile Met Ala Ile Asn Gly Lys Ile Val Thr Asp Tyr Thr Leu Ala  
 180 185 190  
 Glu Ala Asp Ala Ala Leu Gln Lys Ala Trp Asn Gln Gly Gly Asp Trp  
 195 200 205  
 Ile Asp Leu Val Val Ala Val Cys Pro Pro Lys Glu Tyr Asp Asp Glu  
 210 215 220  
 Leu Thr Phe Leu Leu Lys Ser Lys Arg Gly Asn Gln Ile His Ala Leu  
 225 230 235 240  
 Gly Asn Ser Glu Leu Arg Pro His Leu Val Asn Thr Lys Pro Arg Thr  
 245 250 255  
 Ser Leu Glu Arg Gly His Met Thr His Thr Arg Trp His Pro Trp Asp  
 260 265 270  
 Leu Asn Leu Ser Pro Arg Asn Leu Lys Leu Pro Leu Ala Leu Asn Gln  
 275 280 285  
 Gly Gln Ile Arg Asn Ser Ser Gly His Phe Phe Glu Gly Gln Cys Gly  
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 Gly Lys Gly Ala Ala Ser Arg Leu Gly Glu Asp Leu Lys Asp Pro Asp  
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 Ser His Ser Phe Pro Leu Ala Gln  
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<210> 558  
 <211> 2289  
 <212> DNA  
 <213> Homo Sapiens

<400> 558

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&lt;210&gt; 559

&lt;211&gt; 481

&lt;212&gt; PRT

&lt;213&gt; Homo Sapiens

&lt;400&gt; 559

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Met Asp Arg Lys Val Ala Arg Glu Phe Arg His Lys Val Asp Phe Leu
1          5          10          15
Ile Glu Asn Asp Ala Glu Lys Asp Tyr Leu Tyr Asp Val Leu Arg Met
20          25          30
Tyr His Gln Thr Met Asp Val Ala Val Leu Val Gly Asp Leu Lys Leu
35          40          45
Val Ile Asn Glu Pro Ser Arg Leu Pro Leu Phe Asp Ala Ile Arg Pro
50          55          60
Leu Ile Pro Leu Lys His Gln Val Glu Tyr Asp Gln Leu Thr Pro Arg
65          70          75          80
Arg Ser Arg Lys Leu Lys Glu Val Arg Leu Asp Arg Leu His Pro Glu
85          90          95
Gly Leu Gly Leu Ser Val Arg Gly Gly Leu Glu Phe Gly Cys Gly Leu
100          105          110
Phe Ile Ser His Leu Ile Lys Gly Gly Gln Ala Asp Ser Val Gly Leu
115          120          125
Gln Val Gly Asp Glu Ile Val Arg Ile Asn Gly Tyr Ser Ile Ser Ser
130          135          140
Cys Thr His Glu Glu Val Ile Asn Leu Ile Arg Thr Lys Lys Thr Val
145          150          155          160
Ser Ile Lys Val Arg His Ile Gly Leu Ile Pro Val Lys Ser Ser Pro
165          170          175
Asp Glu Pro Leu Thr Trp Gln Tyr Val Asp Gln Phe Val Ser Glu Ser
180          185          190
Gly Gly Val Arg Gly Ser Leu Gly Ser Pro Gly Asn Arg Glu Asn Lys
195          200          205
Glu Lys Lys Val Phe Ile Ser Leu Val Gly Ser Arg Gly Leu Gly Cys
210          215          220
Ser Ile Ser Ser Gly Pro Ile Gln Lys Pro Gly Ile Phe Ile Ser His
225          230          235          240
Val Lys Pro Gly Ser Leu Ser Ala Glu Val Gly Leu Glu Ile Gly Asp
245          250          255
Gln Ile Val Glu Val Asn Gly Val Asp Phe Ser Asn Leu Asp His Lys

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Val	Ala	Ala	Ala	Gly	Arg	Glu	Leu	Phe	Met	Thr	Asp	Arg	Glu	Arg	Leu
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Ala	Glu	Ala	Arg	Gln	Arg	Glu	Leu	Gln	Arg	Gln	Glu	Leu	Leu	Met	Gln
305					310				315					320	
Lys	Arg	Leu	Ala	Met	Glu	Ser	Asn	Lys	Ile	Leu	Gln	Glu	Gln	Gln	Glu
			325					330					335		
Met	Glu	Arg	Gln	Arg	Arg	Lys	Glu	Ile	Ala	Gln	Lys	Ala	Ala	Glu	Glu
	340						345				350				
Asn	Glu	Arg	Tyr	Arg	Lys	Glu	Met	Glu	Gln	Ile	Val	Glu	Glu	Glu	Glu
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	370					375				380					
Leu	Leu	Pro	Lys	Thr	Ile	Thr	Ala	Glu	Val	His	Pro	Val	Pro	Leu	Arg
385					390				395						400
Lys	Pro	Lys	Tyr	Asp	Gln	Gly	Val	Glu	Pro	Glu	Leu	Glu	Pro	Ala	Asp
			405					410					415		
Asp	Leu	Asp	Gly	Thr	Glu	Glu	Gln	Gly	Glu	Gln	Pro	Gln	Glu	Met	
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Leu	Lys	Arg	Met	Val	Val	Tyr	Gln	Asp	Ser	Ile	Gln	Asp	Lys	Ile	Ser
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Gly	Asn	Met	Arg	Lys	Ala	Leu	Thr	Pro	Thr	Leu	Cys	Ser	Pro	Gln	Ser
	450					455				460					
Arg	Ser	Trp	Gly	Arg	Met	Ser	Gly	Ser	Tyr	Ala	Ser	Arg	Arg	Arg	Asp
465					470				475						480
Pro															

&lt;210&gt; 560

&lt;211&gt; 2409

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 560

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&lt;210&gt; 561

&lt;211&gt; 521

&lt;212&gt; PRT

&lt;213&gt; Homo Sapiens

&lt;400&gt; 561

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Met Asp Arg Lys Val Ala Arg Glu Phe Arg His Lys Val Asp Phe Leu
 1             5             10             15
Ile Glu Asn Asp Ala Glu Lys Asp Tyr Leu Tyr Asp Val Leu Arg Met
      20             25             30
Tyr His Gln Thr Met Asp Val Ala Val Leu Val Gly Asp Leu Lys Leu
      35             40             45
Val Ile Asn Glu Pro Ser Arg Leu Pro Leu Phe Asp Ala Ile Arg Pro
      50             55             60
Leu Ile Pro Leu Lys His Gln Val Glu Tyr Asp Gln Leu Thr Pro Arg
      65             70             75             80
Arg Ser Arg Lys Leu Lys Glu Val Arg Leu Asp Arg Leu His Pro Glu
      85             90             95
Gly Leu Gly Leu Ser Val Arg Gly Gly Leu Glu Phe Gly Cys Gly Leu
      100            105            110
Phe Ile Ser His Leu Ile Lys Gly Gln Ala Asp Ser Val Gly Leu
      115            120            125
Gln Val Gly Asp Glu Ile Val Arg Ile Asn Gly Tyr Ser Ile Ser Ser
      130            135            140
Cys Thr His Glu Glu Val Ile Asn Leu Ile Arg Thr Lys Lys Thr Val
      145            150            155            160
Ser Ile Lys Val Arg His Ile Gly Leu Ile Pro Val Lys Ser Ser Pro
      165            170            175
Asp Glu Pro Leu Thr Trp Gln Tyr Val Asp Gln Phe Val Ser Glu Ser
      180            185            190
Gly Gly Val Arg Gly Ser Leu Gly Ser Pro Gly Asn Arg Glu Asn Lys
      195            200            205

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Glu Lys Lys Val Phe Ile Ser Leu Val Gly Ser Arg Gly Leu Gly Cys  
 210 215 220  
 Ser Ile Ser Ser Gly Pro Ile Gln Lys Pro Gly Ile Phe Ile Ser His  
 225 230 235 240  
 Val Lys Pro Gly Ser Leu Ser Ala Glu Val Gly Leu Glu Ile Gly Asp  
 245 250 255  
 Gln Ile Val Glu Val Asn Gly Val Asp Phe Ser Asn Leu Asp His Lys  
 260 265 270  
 Glu Ala Val Asn Val Leu Lys Asn Ser Arg Ser Leu Thr Ile Ser Ile  
 275 280 285  
 Val Ala Ala Ala Gly Arg Glu Leu Phe Met Thr Asp Arg Glu Arg Leu  
 290 295 300  
 Ala Glu Ala Arg Gln Arg Glu Leu Gln Arg Gln Glu Leu Leu Met Gln  
 305 310 315 320  
 Lys Arg Leu Ala Met Glu Ser Asn Lys Ile Leu Gln Glu Gln Gln Glu  
 325 330 335  
 Met Glu Arg Gln Arg Arg Lys Glu Ile Ala Gln Lys Ala Ala Glu Glu  
 340 345 350  
 Asn Glu Arg Tyr Arg Lys Glu Met Glu Gln Ile Val Glu Glu Glu Glu  
 355 360 365  
 Lys Phe Lys Lys Gln Trp Glu Glu Asp Trp Gly Ser Lys Glu Gln Leu  
 370 375 380  
 Leu Leu Pro Lys Thr Ile Thr Ala Glu Val His Pro Val Pro Leu Arg  
 385 390 395 400  
 Lys Pro Lys Tyr Asp Gln Gly Val Glu Pro Glu Leu Glu Pro Ala Asp  
 405 410 415  
 Asp Leu Asp Gly Gly Thr Glu Glu Gln Gly Glu Gln Thr Phe Cys Pro  
 420 425 430  
 Ser Pro Gln Pro Pro Arg Gly Pro Gly Val Ser Thr Ile Ser Lys Pro  
 435 440 445  
 Val Met Val His Gln Glu Pro Asn Phe Ile Tyr Arg Pro Ala Val Lys  
 450 455 460  
 Ser Glu Val Leu Pro Gln Glu Met Leu Lys Arg Met Val Val Tyr Gln  
 465 470 475 480  
 Asp Ser Ile Gln Asp Lys Ile Ser Gly Asn Met Arg Lys Ala Leu Thr  
 485 490 495  
 Pro Thr Leu Cys Ser Pro Gln Ser Arg Ser Trp Gly Arg Met Ser Gly  
 500 505 510  
 Ser Tyr Ala Ser Arg Arg Arg Asp Pro  
 515 520

&lt;210&gt; 562

&lt;211&gt; 1445

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 562

ctccggcagg	gagtcctagc	gcagactttg	cggttcatgg	agagtctctg	ggagacaggc	60
acctgctggac	gctgcagata	agttacgacg	cactgaaaga	tgaaaattct	aagctgagaa	120
gaaagctgaa	tgagggttcag	agcttctctg	aagctcaaac	agaaatgggtg	aggacgcttg	180
agcgggaagtt	agaagcaaaa	atgatcaagg	aggaaagcga	ctaccacgac	ctggagtcgg	240
tggttcagca	ggtggagcag	aacctggagc	tgatgaccaa	acgggctgta	aaggcagaaa	300
accacgtcgt	gaaactaaaa	caggaaatca	gtttgctcca	ggcgcagggtc	tccaacttcc	360
agcgagagaa	tgaagccctg	cggtgccggc	agggtgccag	cctgaccgtg	gtgaagcaga	420
acgccgacgt	ggccctgcag	aacctccggg	tggtcatgaa	cagtgcacag	gcttccatca	480

```

agcaactggg ttccggagct gagacactga atcttgttgc cgaaatcctt aaatctatag      540
acagaatttc tgaagttaaa gacgaggagg aagactcttg aggaccctg ggtgttctca      600
gcatgaagct ccgtgtatac cctgagggtca ccaccgctcg atctaaatgt gcagttgtgt      660
ccttaaatat gcagtcttca cccagagtaa agtgttgatc gcaagagtcc agtgtcgtgc      720
cctcagccag ttcttggcca ccacaatggg agcagccctg gccgagttgt ctctgtggtt      780
tctatgcagc ccttcttggc gaaattcctg cgatcttata gattctaata agctcttgga      840
agacattgtc ataaaagcca gtgattttta gaaaaagagt ggttctggaa tcaatgtttt      900
ccagtcccat cccagaacat cagttgtaag ataagtacaa ttggttgccc ttgatttcat      960
aagtagaaca aacactaaat gtgcctctga gatggccacc ccgggcaggg acctgtgcct     1020
tccgccgatg ctcagggtc cctctggctc ccgggtcact cttgtggccc cagtgggtgg     1080
tccctgcagt catggcctga gtgcgcaggg gccaccgctg ggctgctgct gtcctcctcc     1140
ggggaccacg ggggaacaag gtcacacctt ccgtgctgtg aagctgtcca gatgtgcctc     1200
tttggctggg ggttttgggt gacgtttcaa gtggcatttt gtacaatgca ggtagaattt     1260
caggaatttc aagtatgtgc cggggtntgt caggtcccag ttgcctttnt gacggccccc     1320
ctcagagggg cggcgatgag cactaaatgc ttttttgant attttctat agattttttt     1380
taaaactttt ttttctctct gttccaattg atagctttct tatttaataa attctgtagt     1440
tcacc                                           1445

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&lt;210&gt; 563

&lt;211&gt; 192

&lt;212&gt; PRT

&lt;213&gt; Homo Sapiens

&lt;400&gt; 563

```

Pro Ala Gly Ser Pro Ser Ala Asp Phe Ala Val His Gly Glu Ser Leu
 1             5             10             15
Gly Asp Arg His Leu Arg Thr Leu Gln Ile Ser Tyr Asp Ala Leu Lys
             20             25             30
Asp Glu Asn Ser Lys Leu Arg Arg Lys Leu Asn Glu Val Gln Ser Phe
             35             40             45
Ser Glu Ala Gln Thr Glu Met Val Arg Thr Leu Glu Arg Lys Leu Glu
             50             55             60
Ala Lys Met Ile Lys Glu Glu Ser Asp Tyr His Asp Leu Glu Ser Val
65             70             75             80
Val Gln Gln Val Glu Gln Asn Leu Glu Leu Met Thr Lys Arg Ala Val
             85             90             95
Lys Ala Glu Asn His Val Val Lys Leu Lys Gln Glu Ile Ser Leu Leu
             100            105            110
Gln Ala Gln Val Ser Asn Phe Gln Arg Glu Asn Glu Ala Leu Arg Cys
             115            120            125
Gly Gln Gly Ala Ser Leu Thr Val Val Lys Gln Asn Ala Asp Val Ala
             130            135            140
Leu Gln Asn Leu Arg Val Val Met Asn Ser Ala Gln Ala Ser Ile Lys
145            150            155            160
Gln Leu Val Ser Gly Ala Glu Thr Leu Asn Leu Val Ala Glu Ile Leu
             165            170            175
Lys Ser Ile Asp Arg Ile Ser Glu Val Lys Asp Glu Glu Glu Asp Ser
             180            185            190

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&lt;210&gt; 564

&lt;211&gt; 1226

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 564

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ctgggcccgcg aggcgcggag cttgggagcg gagcccaggc cgtgccgcgc ggcgccatga      60
agggcaagga ggagaaggag ggcggcgac ggctgggcgc tggcggcgga agccccgaga      120
agagcccagag cgcgcaggag ctcaaggagc agggcaatcg tctgttcgtg ggccgaaagt      180
acccggaggc ggcggcctgc tacggccgcg cgatcacccg gaaccgcgtg gtggccgtgt      240
attacaccaa ccgggccttg tgctacctga agatgcagca gcacgagcag gccctggccg      300
actgccggcg cgccctggag ctggacgggc agtctgtgaa ggcgcacttc ttcctggggc      360
agtgccagct ggagatggag agctatgatg aggccatcgc caatctgcag cgagcttaca      420
gcctggccaa ggagcagcgg ctgaacttcg gggacgacat cccagcgcct cttcgaatcg      480
cgaagaagaa gcgctggaac agcattgagg agcggcgcat ccaccaggag agcgagctgc      540
actcctacct ctccaggctc attgccgcgg agcgtgagag ggagctggaa gagtgccagc      600
gaaaccacga gggatgatgag gacgacagcc acgtccgggc ccagcaggcc tgcattgagg      660
ccaagcacga caagtacatg gcggacatgg acgagctttt ttctcagggtg gatgagaaga      720
ggaagaagcg agacatcccc gactacctgt gtggcaagat cagctttgag ctgatgcggg      780
agccgtgcat cacgccagc ggcattcacct acgaccgcaa ggacatcgag gagcacctgc      840
agcgtgtggg tcatTTTTgac ccggtgaccg ggagccccct gacccaggaa cagttcatcc      900
ccaacttggc tatgaaggag gttattgacg cattcatctc tgagaatggc tgggtggagg      960
actactgagg ttccctgccc tacctggcgt cctggctccag gggagccctg ggcagaagcc     1020
cccggccccct aaacatagtt tatgtttttg gccaccccgca ccgcttcccc caagttctgc     1080
tgttggaactc tggactgttt cccctctcag catcgctttt gctgggccgt gattgtcccc     1140
tttgtgggct ggaaaagcag gtgagggtgg gctgggctga ggccattgcc gccactatct     1200
gtgtaataaaa atccgtgagc acgaaa                                     1226

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&lt;210&gt; 565

&lt;211&gt; 303

&lt;212&gt; PRT

&lt;213&gt; Homo Sapiens

&lt;400&gt; 565

```

Met Lys Gly Lys Glu Glu Lys Glu Gly Gly Ala Arg Leu Gly Ala Gly
 1             5             10            15
Gly Gly Ser Pro Glu Lys Ser Pro Ser Ala Gln Glu Leu Lys Glu Gln
      20            25            30
Gly Asn Arg Leu Phe Val Gly Arg Lys Tyr Pro Glu Ala Ala Ala Cys
      35            40            45
Tyr Gly Arg Ala Ile Thr Arg Asn Pro Leu Val Ala Val Tyr Tyr Thr
      50            55            60
Asn Arg Ala Leu Cys Tyr Leu Lys Met Gln Gln His Glu Gln Ala Leu
      65            70            75            80
Ala Asp Cys Arg Arg Ala Leu Glu Leu Asp Gly Gln Ser Val Lys Ala
      85            90            95
His Phe Phe Leu Gly Gln Cys Gln Leu Glu Met Glu Ser Tyr Asp Glu
      100           105           110
Ala Ile Ala Asn Leu Gln Arg Ala Tyr Ser Leu Ala Lys Glu Gln Arg
      115           120           125
Leu Asn Phe Gly Asp Asp Ile Pro Ser Ala Leu Arg Ile Ala Lys Lys
      130           135           140
Lys Arg Trp Asn Ser Ile Glu Glu Arg Arg Ile His Gln Glu Ser Glu
      145           150           155           160
Leu His Ser Tyr Leu Ser Arg Leu Ile Ala Ala Glu Arg Glu Arg Glu
      165           170           175
Leu Glu Glu Cys Gln Arg Asn His Glu Gly Asp Glu Asp Asp Ser His
      180           185           190
Val Arg Ala Gln Gln Ala Cys Ile Glu Ala Lys His Asp Lys Tyr Met
      195           200           205
Ala Asp Met Asp Glu Leu Phe Ser Gln Val Asp Glu Lys Arg Lys Lys

```

210	215	220
Arg Asp Ile Pro Asp Tyr Leu Cys Gly Lys Ile Ser Phe Glu Leu Met		
225	230	235
Arg Glu Pro Cys Ile Thr Pro Ser Gly Ile Thr Tyr Asp Arg Lys Asp		240
	245	250
Ile Glu Glu His Leu Gln Arg Val Gly His Phe Asp Pro Val Thr Gly		255
	260	265
Ser Pro Leu Thr Gln Glu Gln Phe Ile Pro Asn Leu Ala Met Lys Glu		270
	275	280
Val Ile Asp Ala Phe Ile Ser Glu Asn Gly Trp Val Glu Asp Tyr		285
	290	295
		300

<210> 566  
 <211> 1857  
 <212> DNA  
 <213> Homo Sapiens

<400> 566

gtgaggggct cctttgggca ggggtagtgt ttggtgtccc tgtcttgcgt gatattgaca	60
aactgaagct ttcctgcacc actggactta aggaanagtg tactcgtagg cggacagctt	120
tagtggcggg ccggccgctc tcatcccccg taaggagcag agtcctttgt actgaccaag	180
atgagcaaca tctacatcca ggagcctccc acgaatggga aggttttatt gaaaactaca	240
gctggagata ttgacataga gttgtgggtcc aaagaagctc cttaaagcttg cagaaatttt	300
atcccaactt tgtttggaag cttattatga caataccatt tttcatagag ttgtgcctgg	360
tttcatagtc caaggcggag atcctactgg cacagggagt ggtggagagt ctatctatgg	420
agcgccattc aaagatgaat ttcattcacg gttgcgtttt aatcggagag gactggttgc	480
catggcaaat gctggttctc atgataatgg caccactttt ttcttcacac tgggtcgagc	540
agatgaactt aacaataagc ataccatctt tggaaagggt acaggggata cagtatataa	600
catgttgcca ctgtcagaag tagacattga tgatgacgaa agaccacata atccacacaa	660
aataaaaagc tgtgaggttt tgtttaatcc ttttgatgac atcattccaa gggaaattaa	720
aaggctgaaa aaagagaaac cagaggagga agtaaagaaa ttgaaaccca aaggcacaaa	780
aaattttagt ttactttcat ttggagagga agctgaggaa gaagaagagg aagtaaatcg	840
agtttagtcag agcatgaagg gcaaaagcaa aagtagtcag gacttgctta aggatgatcc	900
acatctcagt tctgttccag ttgtagaaag tgaaaaagggt gatgcaccag atttagttga	960
tgatggagaa gatgaaagtg cagagcatga tgaatatatt gatggtgatg aaaagaacct	1020
gatgagagaa agaattgcc aaaaattaaa aaaggacaca agtgcgaaatg ttaaatacagc	1080
tggagaagga gaagtggaga agaaatcagt cagccgcagt gaagagctca gaaaagaagc	1140
aagacaatta aaacgggaac tcttagcagc aaaacaaaaa aaagtagaaa atgcagcaaa	1200
acaagcagaa aaaagaagtg aagaggaaga agcccctcca gatggtgctg ttgccgaata	1260
cagaagagaa aagcaaaagt atgaagcttt gaggaagcaa cagtcaaaga agggaacttc	1320
ccgggaagat cagacccttg cactgctgaa ccagttttaa tctaaactca ctcaagcaat	1380
tgctgaaaca cctgaaaatg acattcctga aacagaagta gaagatgatg aaggatggat	1440
gtcacatgta cttcagtttg aggataaaag cagaaaagtg aaagatgcaa gcatgcaaga	1500
ctcagatata tttgaaatct atgatcctcg gaatccagtg aataaaaagaa ggaggggaaga	1560
aagcaaaaag ctgatgagag agaaaaaaga aagaagataa aatgagaata atgataacca	1620
gaacttgctg gaaatgtgcc tacaatggcc ttgtaacagc cattgttccc aacagcatca	1680
cttaggggtg tgaaaagaag tatttttgaa cctgttgtct ggttttgaaa aacaattatc	1740
ttgttttgca aattgtggaa tgatgtaagc aaatgctttt ggttactggg acatgtgttt	1800
tttcctagct gaccttttat attgctaaat ctgaaataaa ataactttcc ttccaaa	1857

<210> 567  
 <211> 372  
 <212> PRT  
 <213> Homo Sapiens



<400> 567

Met Ala Asn Ala Gly Ser His Asp Asn Gly Thr His Phe Phe Phe Thr  
 1 5 10 15  
 Leu Gly Arg Ala Asp Glu Leu Asn Asn Lys His Thr Ile Phe Gly Lys  
 20 25 30  
 Val Thr Gly Asp Thr Val Tyr Asn Met Leu Arg Leu Ser Glu Val Asp  
 35 40 45  
 Ile Asp Asp Asp Glu Arg Pro His Asn Pro His Lys Ile Lys Ser Cys  
 50 55 60  
 Glu Val Leu Phe Asn Pro Phe Asp Asp Ile Ile Pro Arg Glu Ile Lys  
 65 70 75 80  
 Arg Leu Lys Lys Glu Lys Pro Glu Glu Glu Val Lys Lys Leu Lys Pro  
 85 90 95  
 Lys Gly Thr Lys Asn Phe Ser Leu Leu Ser Phe Gly Glu Glu Ala Glu  
 100 105 110  
 Glu Glu Glu Glu Glu Val Asn Arg Val Ser Gln Ser Met Lys Gly Lys  
 115 120 125  
 Ser Lys Ser Ser His Asp Leu Leu Lys Asp Asp Pro His Leu Ser Ser  
 130 135 140  
 Val Pro Val Val Glu Ser Glu Lys Gly Asp Ala Pro Asp Leu Val Asp  
 145 150 155 160  
 Asp Gly Glu Asp Glu Ser Ala Glu His Asp Glu Tyr Ile Asp Gly Asp  
 165 170 175  
 Glu Lys Asn Leu Met Arg Glu Arg Ile Ala Lys Lys Leu Lys Lys Asp  
 180 185 190  
 Thr Ser Ala Asn Val Lys Ser Ala Gly Glu Gly Glu Val Glu Lys Lys  
 195 200 205  
 Ser Val Ser Arg Ser Glu Glu Leu Arg Lys Glu Ala Arg Gln Leu Lys  
 210 215 220  
 Arg Glu Leu Leu Ala Ala Lys Gln Lys Lys Val Glu Asn Ala Ala Lys  
 225 230 235 240  
 Gln Ala Glu Lys Arg Ser Glu Glu Glu Glu Ala Pro Pro Asp Gly Ala  
 245 250 255  
 Val Ala Glu Tyr Arg Arg Glu Lys Gln Lys Tyr Glu Ala Leu Arg Lys  
 260 265 270  
 Gln Gln Ser Lys Lys Gly Thr Ser Arg Glu Asp Gln Thr Leu Ala Leu  
 275 280 285  
 Leu Asn Gln Phe Lys Ser Lys Leu Thr Gln Ala Ile Ala Glu Thr Pro  
 290 295 300  
 Glu Asn Asp Ile Pro Glu Thr Glu Val Glu Asp Asp Glu Gly Trp Met  
 305 310 315 320  
 Ser His Val Leu Gln Phe Glu Asp Lys Ser Arg Lys Val Lys Asp Ala  
 325 330 335  
 Ser Met Gln Asp Ser Asp Thr Phe Glu Ile Tyr Asp Pro Arg Asn Pro  
 340 345 350  
 Val Asn Lys Arg Arg Arg Glu Glu Ser Lys Lys Leu Met Arg Glu Lys  
 355 360 365  
 Lys Glu Arg Arg  
 370

&lt;210&gt; 568

&lt;211&gt; 1537

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 568

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gccgcgcgcc gatcggtcgt taccgcgagg cgctgggtggc cttcaggctg gacgggcgcgg      60
gtcagccctg gttcgcgcggc ttctgggtct ttgaacagcc gcgatgtcga tcttcacccc      120
caccaaccag atccgcctaa ccaatgtggc cgtgggtacgg atgaagcgtg ccgggaagcg      180
cttcgaaatc gcctgctaca aaaacaaggt cgctcggtgg cgagcggcg tggaaaaaga      240
cctcgatgaa gttctgcaga cccactcagt gtttgtaaat gtttctaaag gtcagggttg      300
caaaaaggaa gatctcatca gtgcgttttg aacagatgac caaactgaaa tctgtaagca      360
gattttgact aaaggagaag ttcaagtatc agataaagaa agacacacac aactggagca      420
gatgttttagg gacattgcaa ctattgtggc agacaaatgt gtgaatcctg aaacaaagag      480
accatacacc gtgatcctta ttgagagagc catgaaggac atccactatt cggtgaaaac      540
caacaagagt acaaaacagc aggcctttgga agtgataaag cagttaaaag agaaaatgaa      600
gatagaacgt gtcacatga agcttcggtt catccttcca gtcaatgaag gcaagaactg      660
aaagaaaagc tcaagccact gatcaaggtc atagaaagtg aagattatgg ccaacagtta      720
gaaatcgat gtctgattga cccgggctgc ttccgagaaa ttgatgagct aataaaaaag      780
gaaactaaag gcaaaggttc tttggaagta ctcaatctga aagatgtaga agaaggagat      840
gagaaatttg aatgacaccc atcaatctct tcacctctaa aacactaaag tgtttccggt      900
tccgacggca ctgtttcatg tctgtggtct gccaaatact tgcttaaact atttgacatt      960
ttctatcttt gtgttaacag tggacacagc aaggctttcc tacataagta taataatgtg      1020
ggaatgattt ggttttaatt ataaactggg gtctaaatcc taaagcaaaa ttgaaactcc      1080
aagatgcaaa gtccagagtg gcattttgct actctgtctc atgccttgat agctttccaa      1140
aatgaaagt tcttgangca gctcttggtg gtgaaaagt atttgtagag tagagtaaga      1200
ttattagggg tatgtctata caacaaaagg gggggtcttt ctaaaaaaag aaaacatatg      1260
atgcttcatt tctacttaat ggaacttggt ttctgagggt cattatggta tcgtaatgta      1320
aagcttggat gatgttcctg attatttgag gaacagatat aggaaaattg tgccgggaatt      1380
acctttcatt gaacatgctg ccataaatta gggtattttt ggtaaaaaaa taaaagtcaa      1440
ttatttttaa tttttaaagt ttataatata tattaatata ggtaaaattg tatgtaatca      1500
ataaaaccaa ttttatgttt attaaactta aaaaaaa      1537

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&lt;210&gt; 569

&lt;211&gt; 210

&lt;212&gt; PRT

&lt;213&gt; Homo Sapiens

&lt;400&gt; 569

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Ala Ala Arg Arg Ser Val Val Thr Ala Arg Arg Trp Trp Pro Ser Gly
 1          5          10          15
Trp Thr Ala Arg Val Ser Pro Gly Ser Pro Ala Ser Gly Ser Leu Asn
      20          25          30
Ser Arg Asp Val Asp Leu His Pro His Gln Pro Asp Pro Pro Asn Gln
      35          40          45
Cys Gly Arg Gly Thr Asp Glu Ala Cys Arg Glu Ala Leu Arg Asn Arg
      50          55          60
Leu Leu Gln Lys Gln Val Val Gly Trp Arg Ser Gly Val Glu Lys Asp
      65          70          75          80
Leu Asp Glu Val Leu Gln Thr His Ser Val Phe Val Asn Val Ser Lys
      85          90          95
Gly Gln Val Ala Lys Lys Glu Asp Leu Ile Ser Ala Phe Gly Thr Asp
      100          105          110
Asp Gln Thr Glu Ile Cys Lys Gln Ile Leu Thr Lys Gly Glu Val Gln
      115          120          125
Val Ser Asp Lys Glu Arg His Thr Gln Leu Glu Gln Met Phe Arg Asp
      130          135          140
Ile Ala Thr Ile Val Ala Asp Lys Cys Val Asn Pro Glu Thr Lys Arg
      145          150          155          160
Pro Tyr Thr Val Ile Leu Ile Glu Arg Ala Met Lys Asp Ile His Tyr

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```
<210> 570
<211> 1211
<212> DNA
<213> Homo Sapiens
```

```
<210> 571
<211> 354
<212> PRT
<213> Homo Sapiens
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-301-

100 105 110  
 Pro His Leu Ser Ser Val Pro Val Val Glu Ser Glu Lys Gly Asp Ala  
 115 120 125  
 Ala Asp Leu Val Asp Asp Gly Glu Asp Glu Ser Ala Glu His Asp Glu  
 130 135 140  
 Tyr Ile Asp Gly Asp Glu Lys Asn Leu Met Arg Glu Arg Ile Ala Lys  
 145 150 155 160  
 Lys Leu Lys Lys Asp Thr Ser Ala Asn Val Lys Ser Ala Gly Glu Gly  
 165 170 175  
 Glu Val Glu Lys Lys Ser Val Ser Arg Ser Glu Glu Leu Arg Lys Glu  
 180 185 190  
 Ala Arg Gln Leu Lys Arg Glu Leu Leu Ala Ala Glu Gln Lys Lys Val  
 195 200 205  
 Glu Asn Ala Ala Lys Gln Ala Glu Lys Arg Ser Glu Glu Glu Glu Ala  
 210 215 220  
 Pro Pro Asp Gly Ala Val Ala Glu Tyr Arg Arg Glu Lys Gln Lys Tyr  
 225 230 235 240  
 Glu Ala Leu Arg Lys Gln Gln Ser Lys Lys Gly Thr Ser Arg Glu Asp  
 245 250 255  
 Gln Thr Leu Ala Leu Leu Asn Gln Phe Lys Ser Lys Leu Thr Gln Ala  
 260 265 270  
 Ile Ala Glu Thr Pro Glu Asn Asp Ile Pro Glu Thr Glu Val Glu Asp  
 275 280 285  
 Asp Glu Gly Trp Met Ser His Val Leu Gln Phe Glu Asp Lys Ser Arg  
 290 295 300  
 Lys Val Lys Asp Ala Ser Met Gln Asp Ser Asp Thr Phe Glu Ile Tyr  
 305 310 315 320  
 Asp Pro Arg Asn Pro Val Asn Lys Arg Arg Arg Glu Glu Ser Lys Lys  
 325 330 335  
 Leu Met Arg Glu Lys Lys Glu Arg Arg Ile Leu Pro Val Asn Glu Gly  
 340 345 350  
 Lys Asn

<210> 572  
 <211> 604  
 <212> DNA  
 <213> Homo Sapiens

<400> 572  
 ccttcggcaa aaaatttttg tcccaacttt ttgttccatt ccaaaagggc ttaccttcat 60  
 tcccttttagc aacagggccc ccaagaagct cccgttcatt cacccttacc ttggccccc 120  
 gggttgaccc ccaaaggctc ccttacccca aagtgggtgg ttgaataaat cttctcagtt 180  
 ccctggctcc caaggcccat tgaagaagat tgtacaaggc gtgcctcaag taccctgagt 240  
 ggaaacagaa gcacctgcct cacttcaagc cgtggctgca cccggagcag agcccggtgc 300  
 cgagcctggc gctgtcggag ctgtcgggtgc agcatgcgga ctactggag aacatcgacg 360  
 agagcgcggt ggccgagagc agagaggagc ggatgggagg cgcgggcggc gagggcagcg 420  
 acgacgacac cttcacctga gcccgcaccg cttcagggac ggagacagga ccgggcgagc 480  
 cctggggcgg cggcgcgtcc tgcactttct cccctcccc acccggcacc tgggtggcacc 540  
 gggccaggcc caggcgggtg ctgcagcctg gctggacaga gcccaataaa cggtatccac 604  
 agcc

<210> 573  
 <211> 195  
 <212> PRT

&lt;213&gt; Homo Sapiens

&lt;400&gt; 573

```

Leu Arg Gln Lys Ile Leu Val Pro Thr Phe Cys Ser Ile Pro Lys Gly
 1           5           10           15
Leu Thr Phe Ile Pro Phe Ser Asn Arg Ala Pro Lys Lys Leu Pro Phe
          20           25           30
Ile His Pro Tyr Leu Gly Pro Gln Val Gly Pro Pro Lys Ala Pro Leu
          35           40           45
Pro Gln Ser Gly Trp Leu Asn Lys Ser Ser Gln Phe Pro Gly Ser Gln
          50           55           60
Gly Pro Leu Lys Lys Ile Val Gln Gly Val Pro Gln Val Pro Arg Val
65           70           75           80
Glu Thr Glu Ala Pro Ala Ser Leu Gln Ala Val Ala Ala Pro Gly Ala
          85           90           95
Glu Pro Val Ala Glu Pro Gly Ala Val Gly Ala Val Gly Ala Ala Cys
          100          105          110
Gly Leu Thr Gly Glu His Arg Arg Glu Arg Gly Gly Arg Glu Gln Arg
          115          120          125
Gly Ala Asp Gly Arg Arg Gly Arg Arg Gly Gln Arg Arg Arg His Leu
          130          135          140
His Leu Ser Pro His Arg Phe Arg Asp Gly Asp Arg Thr Gly Arg Ala
145          150          155          160
Leu Gly Arg Arg Pro Leu Leu His Phe Leu Pro Ser Pro Thr Arg His
          165          170          175
Leu Val Ala Pro Gly Gln Ala Gln Ala Gly Ala Ala Ala Trp Leu Asp
          180          185          190
Arg Ala Gln
          195

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&lt;210&gt; 574

&lt;211&gt; 742

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 574

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ggctgccggc aatggggggg cctggccccg gccctgtga ggaccccgcg ggtgctgggg      180
gagcaggtgc agggggctcc gagccctgg tgactgtcac cgtgcagtgc gccttcacag      240
tggccctgag ggcaggaaga ggagccgacc ttccagcct gcgggcactg ctggggccaag      300
ccttccttca ccaggcccag cttgggcaat tcagttacct agccccaggt gaggacgggc      360
actgggtccc catccccgag gaggagtcgc tgcagagggc ctggcaggac gcagctgcct      420
gccccagggg gctgcagctg cagtgcaggg gagccggggg tcggccgggtc ctttaccagg      480
tggtggccca gcacagatac tccgcccagg ggccagagga cctgggcttc cgacaggggg      540
acacggtgga cgtcctgtgt gaagtggacc aggcattggc ggagggccac tgtgacggcc      600
gcateggcat cttcccccaag tgcttcgtgg tccccgccg ccctcgcatg tcaggagccc      660
ccggccgcct gccccgatcc cagcaggagg atcagcccta atgatgctgt gtccatgatg      720
cttttaataa aaacaacccc ca                                742

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&lt;210&gt; 575

&lt;211&gt; 232

&lt;212&gt; PRT

&lt;213&gt; Homo Sapiens

<400> 575

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 Thr Ser Thr Ala Tyr Gln Glu Gln Arg Pro Gln Val Glu Gln Val Gly  
 20 25 30  
 Lys Val Ala Pro Leu Ser Pro Gly Leu Pro Ala Met Gly Gly Pro Gly  
 35 40 45  
 Pro Gly Pro Cys Glu Asp Pro Ala Gly Ala Gly Gly Ala Gly Ala Gly  
 50 55 60  
 Gly Ser Glu Pro Leu Val Thr Val Thr Val Gln Cys Ala Phe Thr Val  
 65 70 75 80  
 Ala Leu Arg Ala Gly Arg Gly Ala Asp Leu Ser Ser Leu Arg Ala Leu  
 85 90 95  
 Leu Gly Gln Ala Phe Leu His Gln Ala Gln Leu Gly Gln Phe Ser Tyr  
 100 105 110  
 Leu Ala Pro Gly Glu Asp Gly His Trp Val Pro Ile Pro Glu Glu Glu  
 115 120 125  
 Ser Leu Gln Arg Ala Trp Gln Asp Ala Ala Ala Cys Pro Arg Gly Leu  
 130 135 140  
 Gln Leu Gln Cys Arg Gly Ala Gly Gly Arg Pro Val Leu Tyr Gln Val  
 145 150 155 160  
 Val Ala Gln His Arg Tyr Ser Ala Gln Gly Pro Glu Asp Leu Gly Phe  
 165 170 175  
 Arg Gln Gly Asp Thr Val Asp Val Leu Cys Glu Val Asp Gln Ala Trp  
 180 185 190  
 Leu Glu Gly His Cys Asp Gly Arg Ile Gly Ile Phe Pro Lys Cys Phe  
 195 200 205  
 Val Val Pro Ala Gly Pro Arg Met Ser Gly Ala Pro Gly Arg Leu Pro  
 210 215 220  
 Arg Ser Gln Gln Gly Asp Gln Pro  
 225 230

<210> 576

<211> 1087

<212> DNA

<213> Homo Sapiens

<400> 576

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 ttcaaacaac cggtaaccac agtcacaaat catcctagta ataaagtga atcagaccca 180  
 caacgaatga atgaacagcc acgtcagctt ttctgggaga agaggctaca aggacttagt 240  
 gcatcagatg taacagaaca aattataaaa accatggaac taccacaaagg tcttcaagga 300  
 gttggtccag gtagcaatga tgagaccctt ttatctgctg ttgccagtgc tttgcacaca 360  
 agctctgcgc caatcacagg gcaagtctcc gctgctgtgg aaaagaaccc tgctgtttgg 420  
 cttaacacat ctcaaccctt ctgcaaagct ttattgttca cagatgaaga catcaggaaa 480  
 caggaagagc gagtacagca agtacgcaag aaattggaag aagcactgat ggcagacatc 540  
 ttgtcgcgag ctgctgatac agaagagatg gatattgaaa tggacagtgg agatgaagcc 600  
 taagaatatg atcaggtaac ttctgaccga ctttcccca gagaaaattc ctagaaattg 660  
 aacaaaaatg tttccactgg cttttgcttg taagaaaaaa aatgtacccg agcacataga 720  
 gctttttta atgactaacc aatgcctttt tagatgtatt tttgatgtat atatctatta 780  
 ttcaaaaaat catgtttatt ttgagtccta ggacttaaaa ttagtctttt gtaatatcaa 840  
 gcaggaccct aagatgaagc tgagcttttg atgccaggtg caatttactg gaaatgtagc 900  
 acttacgtaa aacatttggt tccccacag ttttaataag aacagatcag gaattctaaa 960  
 taaatttccc agttaaagat tattgtgact tcaactgtata taaacatatt ttatactttt 1020

attgaaaggg gacacctgta cattcttcca tcgtcactgt aaagacaaat aaatgattat 1080  
attcaca 1087

<210> 577  
<211> 200  
<212> PRT  
<213> Homo Sapiens

<400> 577  
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Asp Pro Leu Asn Gln Asn Lys Gly Lys Pro Asp Leu Asn Thr Thr Leu  
20 25 30  
Pro Ile Arg Gln Thr Ala Ser Ile Phe Lys Gln Pro Val Thr Lys Val  
35 40 45  
Thr Asn His Pro Ser Asn Lys Val Lys Ser Asp Pro Gln Arg Met Asn  
50 55 60  
Glu Gln Pro Arg Gln Leu Phe Trp Glu Lys Arg Leu Gln Gly Leu Ser  
65 70 75 80  
Ala Ser Asp Val Thr Glu Gln Ile Ile Lys Thr Met Glu Leu Pro Lys  
85 90 95  
Gly Leu Gln Gly Val Gly Pro Gly Ser Asn Asp Glu Thr Leu Leu Ser  
100 105 110  
Ala Val Ala Ser Ala Leu His Thr Ser Ser Ala Pro Ile Thr Gly Gln  
115 120 125  
Val Ser Ala Ala Val Glu Lys Asn Pro Ala Val Trp Leu Asn Thr Ser  
130 135 140  
Gln Pro Leu Cys Lys Ala Phe Ile Val Thr Asp Glu Asp Ile Arg Lys  
145 150 155 160  
Gln Glu Glu Arg Val Gln Gln Val Arg Lys Lys Leu Glu Glu Ala Leu  
165 170 175  
Met Ala Asp Ile Leu Ser Arg Ala Ala Asp Thr Glu Glu Met Asp Ile  
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Glu Met Asp Ser Gly Asp Glu Ala  
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<210> 578  
<211> 2569  
<212> DNA  
<213> Homo Sapiens

<400> 578  
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tgtttctcat ataaatgacc ttccagactt ttatgttcaa ctaatagaag atgaagctga 180  
aattagtcac ctttcagaga gattaaacag tgttaaaaca aggcccgaat attatgtagg 240  
tccacctttg caaagaggag atatgatatg tgctgttttc ccagaagata atttatggta 300  
tcgtgctgtg atcaaggagc aacaacccaa tgaccttctc tctgtgcagt ttatagatta 360  
tggcaatgtt tctgtggttc atactaacia aataggtagg cttgaccttg ttaatgcaat 420  
attgccgggg ttgtgcattc attgtctcct gcagggattt gaggttctctg acaataaaaa 480  
ttctaagaaa atgatgcatt acttttccca acggaccagc gaggtctgca taagatgtga 540  
atttgttaaa tttcaagaca gatgggaagt tattcttgct gatgaacatg ggatcatagc 600  
agatgatatg attagcaggt atgctctcag tgaaaaatct caagtagaac tttctacca 660  
agtaattaaa agtgccagtt caaagtctgt taacaaatca gacattgaca cttcagtatt 720  
tcttaactgg tataatccag aaaaaaaaaat gataagagct tatgccactg tgatagatgg 780

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acctgagtag ttttgggtgtc agtttgctga tacggagaaa cttcagtggt tagaagtaga      840
agtacagact gctggagAAC aggtagcaga caggagaaat tgtatcccat gtccttatat      900
tggagatcct tgtatagtaa gatacagaga agatggacat tattataggg cacttatcac      960
taatatattgt gaagattatc ttgtatctgt caggcttggt gactttggaa acattgaaga     1020
ctgtgtggac ccaaaagcac tctggggccat tccttctgaa cttctgtcgg ttcccatgca     1080
agccttttcca tgttgccctc cagggtttta catttcagaa ggattatggt ctcaagaggg     1140
aaatgactat ttctatgaaa taataacaga agatgtgttg gaaataacaa tactagaaat     1200
cagaagggat gtttgtgata tcccttttagc aattgttgac ttgaaaagca aaggtaaaag     1260
tattaatgag aaaatggaga aatattctaa gactgggtatt aaaagtgtct tccctatga     1320
aaatattgac tcagagataa agcagactct tgggtcctac aatcttgatg taggacttaa     1380
gaaattaagt aataaagctg tacaaaataa aatatatatg gaacaacaga cagatgagct     1440
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atacctgatt acaggattta acacattact accacatgct aatgaaacaa aggagatact     1680
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cccggtgcca ccgaatgtgc cactctccca agagtgtgtc acaaaaaggcg ccatggagct     1860
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tctaaatgtg ttgtgtgggtc aagtntaaga aacanatggt ctaaagtgtg gatttttaga     2340
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ttggaggtga tggagattta accgtggatn tatactgtgt gccaatcagt cagaagctgc     2520
centgaacaa gtggcatctt acgcagacca acagagtatt tgagaaaat      2569

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&lt;210&gt; 579

&lt;211&gt; 752

&lt;212&gt; PRT

&lt;213&gt; Homo Sapiens

&lt;400&gt; 579

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Arg Val Lys Ala Thr Leu Ser Glu Arg Lys Ile Gly Asp Ser Cys Asp
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Lys Asp Leu Pro Leu Lys Phe Cys Glu Phe Pro Gln Lys Thr Ile Met
          20          25          30
Pro Gly Phe Lys Thr Thr Val Tyr Val Ser His Ile Asn Asp Leu Ser
          35          40          45
Asp Phe Tyr Val Gln Leu Ile Glu Asp Glu Ala Glu Ile Ser His Leu
          50          55          60
Ser Glu Arg Leu Asn Ser Val Lys Thr Arg Pro Glu Tyr Tyr Val Gly
          65          70          75          80
Pro Pro Leu Gln Arg Gly Asp Met Ile Cys Ala Val Phe Pro Glu Asp
          85          90          95
Asn Leu Trp Tyr Arg Ala Val Ile Lys Glu Gln Gln Pro Asn Asp Leu
          100         105         110
Leu Ser Val Gln Phe Ile Asp Tyr Gly Asn Val Ser Val Val His Thr
          115         120         125
Asn Lys Ile Gly Arg Leu Asp Leu Val Asn Ala Ile Leu Pro Gly Leu
          130         135         140

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 165 170 175  
 Ile Arg Cys Glu Phe Val Lys Phe Gln Asp Arg Trp Glu Val Ile Leu  
 180 185 190  
 Ala Asp Glu His Gly Ile Ile Ala Asp Asp Met Ile Ser Arg Tyr Ala  
 195 200 205  
 Leu Ser Glu Lys Ser Gln Val Glu Leu Ser Thr Gln Val Ile Lys Ser  
 210 215 220  
 Ala Ser Ser Lys Ser Val Asn Lys Ser Asp Ile Asp Thr Ser Val Phe  
 225 230 235 240  
 Leu Asn Trp Tyr Asn Pro Glu Lys Lys Met Ile Arg Ala Tyr Ala Thr  
 245 250 255  
 Val Ile Asp Gly Pro Glu Tyr Phe Trp Cys Gln Phe Ala Asp Thr Glu  
 260 265 270  
 Lys Leu Gln Cys Leu Glu Val Glu Val Gln Thr Ala Gly Glu Gln Val  
 275 280 285  
 Ala Asp Arg Arg Asn Cys Ile Pro Cys Pro Tyr Ile Gly Asp Pro Cys  
 290 295 300  
 Ile Val Arg Tyr Arg Glu Asp Gly His Tyr Tyr Arg Ala Leu Ile Thr  
 305 310 315 320  
 Asn Ile Cys Glu Asp Tyr Leu Val Ser Val Arg Leu Val Asp Phe Gly  
 325 330 335  
 Asn Ile Glu Asp Cys Val Asp Pro Lys Ala Leu Trp Ala Ile Pro Ser  
 340 345 350  
 Glu Leu Leu Ser Val Pro Met Gln Ala Phe Pro Cys Cys Leu Ser Gly  
 355 360 365  
 Phe Asn Ile Ser Glu Gly Leu Cys Ser Gln Glu Gly Asn Asp Tyr Phe  
 370 375 380  
 Tyr Glu Ile Ile Thr Glu Asp Val Leu Glu Ile Thr Ile Leu Glu Ile  
 385 390 395 400  
 Arg Arg Asp Val Cys Asp Ile Pro Leu Ala Ile Val Asp Leu Lys Ser  
 405 410 415  
 Lys Gly Lys Ser Ile Asn Glu Lys Met Glu Lys Tyr Ser Lys Thr Gly  
 420 425 430  
 Ile Lys Ser Ala Leu Pro Tyr Glu Asn Ile Asp Ser Glu Ile Lys Gln  
 435 440 445  
 Thr Leu Gly Ser Tyr Asn Leu Asp Val Gly Leu Lys Lys Leu Ser Asn  
 450 455 460  
 Lys Ala Val Gln Asn Lys Ile Tyr Met Glu Gln Gln Thr Asp Glu Leu  
 465 470 475 480  
 Ala Glu Ile Thr Glu Lys Asp Val Asn Ile Ile Gly Thr Lys Pro Ser  
 485 490 495  
 Asn Phe Arg Asp Pro Lys Thr Asp Asn Ile Cys Glu Gly Phe Glu Asn  
 500 505 510  
 Pro Cys Lys Asp Lys Ile Asp Thr Glu Glu Leu Glu Gly Glu Leu Glu  
 515 520 525  
 Cys His Leu Val Asp Lys Ala Glu Phe Asp Asp Lys Tyr Leu Ile Thr  
 530 535 540  
 Gly Phe Asn Thr Leu Leu Pro His Ala Asn Glu Thr Lys Glu Ile Leu  
 545 550 555 560  
 Glu Leu Asn Ser Leu Glu Val Pro Leu Ser Pro Asp Asp Glu Ser Lys  
 565 570 575  
 Glu Phe Leu Glu Leu Glu Ser Ile Glu Leu Gln Asn Ser Leu Val Val

	580		585		590										
Asp	Glu	Glu	Lys	Gly	Glu	Leu	Ser	Pro	Val	Pro	Pro	Asn	Val	Pro	Leu
	595						600					605			
Ser	Gln	Glu	Cys	Val	Thr	Lys	Gly	Ala	Met	Glu	Leu	Phe	Thr	Leu	Gln
	610					615					620				
Leu	Pro	Leu	Ser	Cys	Glu	Ala	Glu	Lys	Gln	Pro	Glu	Leu	Glu	Leu	Pro
625					630					635					640
Thr	Ala	Gln	Leu	Pro	Leu	Asp	Asp	Lys	Met	Asp	Pro	Leu	Ser	Leu	Gly
			645						650					655	
Val	Ser	Gln	Lys	Ala	Gln	Glu	Ser	Met	Cys	Thr	Glu	Asp	Met	Arg	Lys
			660					665					670		
Ser	Ser	Cys	Val	Glu	Ser	Phe	Asp	Asp	Gln	Arg	Arg	Met	Ser	Leu	His
	675						680					685			
Leu	His	Gly	Ala	Asp	Cys	Asp	Pro	Lys	Thr	Gln	Asn	Glu	Met	Asn	Ile
	690					695					700				
Cys	Glu	Glu	Glu	Phe	Val	Glu	Tyr	Lys	Asn	Arg	Asp	Ala	Ile	Ser	Ala
705					710					715					720
Leu	Met	Pro	Phe	Ser	Leu	Arg	Lys	Lys	Ala	Val	Met	Glu	Ala	Ser	Thr
				725					730					735	
Ile	Met	Val	Tyr	Gln	Ile	Ile	Phe	Gln	Asn	Tyr	Arg	Thr	Pro	Thr	Leu
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<210> 580  
 <211> 2077  
 <212> DNA  
 <213> Homo Sapiens

<400> 580

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gaggtgactc	gagcagtgat	gaggataaag	aataacatga	aactcctgtg	gaagtagaac	180
tcatgactca	ggttgaccaa	gaggatatca	ctcttcagag	tggcagagat	gaactaaatg	240
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gaaagaaact	ccgttccttg	aggttataac	tcattgagtta	caagactttg	ctgtagatga	900
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aactgaacag	tgaagtggct	tgattgctta	aactatttct	ctggttaagtc	tactgtatat	1620

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tcctaaagta tttgtggaca gttaaatgct aattatatac atctgtagtt attctacatt 1800
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gtgaagtggc ttgattgctt aaactattga cttggtaagt ctactgtata taacatctaa 1920
tatatatata ttataggcca gctacaagggt gtttaaatat ttaggattgt gtcttgaaaa 1980
ctaagtattg gagtggattt tcttctgctt tcattgatac ttgtcagaaa aaaatattag 2040
accaaaatgt aaaatataag taataattct catgaaa 2077

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&lt;210&gt; 581

&lt;211&gt; 312

&lt;212&gt; PRT

&lt;213&gt; Homo Sapiens

&lt;400&gt; 581

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Arg Gly Arg Asp Leu Asn Tyr Pro Asp Thr Thr Ile Asp Leu Ser His
1          5          10          15
Leu Gln Pro Gln Arg Ser Ile Gln Lys Leu Ala Ser Lys Glu Glu Ser
20          25          30
Ser Asn Ser Ser Asp Ser Lys Ser Gln Ser Arg Arg His Leu Ser Ala
35          40          45
Lys Glu Arg Arg Glu Met Lys Lys Lys Lys Leu Pro Ser Asp Ser Gly
50          55          60
Asp Leu Glu Ala Leu Glu Gly Lys Asp Lys Glu Lys Glu Ser Thr Val
65          70          75          80
His Ile Glu Thr His Gln Asn Thr Ser Lys Asn Val Ala Ala Val Gln
85          90          95
Pro Met Lys Arg Gly Gln Lys Ser Lys Met Lys Lys Met Lys Glu Lys
100         105         110
Tyr Lys Asp Gln Asp Glu Glu Asp Arg Glu Leu Ile Met Lys Leu Leu
115         120         125
Gly Ser Ala Gly Ser Asn Lys Glu Glu Lys Gly Lys Lys Gly Lys Lys
130         135         140
Gly Lys Thr Lys Asp Glu Pro Val Lys Lys Gln Pro Gln Lys Pro Arg
145         150         155         160
Gly Gly Gln Arg Val Ser Asp Asn Ile Lys Lys Glu Thr Pro Phe Leu
165         170         175
Glu Val Ile Thr His Glu Leu Gln Asp Phe Ala Val Asp Asp Pro His
180         185         190
Asp Asp Lys Glu Glu Gln Asp Leu Asp Gln Gln Gly Asn Glu Glu Asn
195         200         205
Leu Phe Asp Ser Leu Thr Gly Gln Pro His Pro Glu Asp Val Leu Leu
210         215         220
Phe Ala Ile Pro Ile Cys Ala Pro Tyr Thr Thr Met Thr Asn Tyr Lys
225         230         235         240
Tyr Lys Val Lys Leu Thr Pro Gly Val Gln Lys Lys Gly Lys Ala Ala
245         250         255
Lys Thr Ala Leu Asn Ser Phe Met His Ser Lys Glu Ala Thr Ala Arg
260         265         270
Glu Lys Asp Leu Phe Arg Ser Val Lys Asp Thr Asp Leu Ser Arg Asn
275         280         285
Ile Pro Gly Lys Val Lys Ser Val Cys Thr Gln Ser Ser Glu Arg Lys
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<210> 582  
 <211> 3309  
 <212> DNA  
 <213> Homo Sapiens

<400> 582

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ttcaaaagat	ttcatggccg	agcattcaat	gaccccttca	ttcaaaagga	gaaggaaaac	300
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tgtttaagac	ttatgaatga	catgacagct	ggtgctttga	attacggaat	ttataagcag	600
gatctcccaa	gcctggatga	gaaacctcgg	atagtgggtt	ttgttgatat	gggacattca	660
gcttttcaag	tgtctgcttg	tgcttttaac	aagggaat	tgaaggtagt	gggaacagct	720
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gtcatttct 3309

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&lt;210&gt; 583

&lt;211&gt; 872

&lt;212&gt; PRT

&lt;213&gt; Homo Sapiens

&lt;400&gt; 583

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Arg Arg Pro Arg Pro Glu Ala Glu Ala Asp Arg Glu Pro Ala Met Ser
 1           5           10           15
Val Val Gly Leu Asp Val Gly Ser Gln Ser Cys Tyr Ile Ala Val Ala
          20           25           30
Arg Ala Gly Gly Ile Glu Thr Ile Ala Asn Glu Phe Ser Asp Arg Cys
          35           40           45
Thr Pro Ser Val Ile Ser Phe Gly Ser Lys Asn Arg Thr Ile Gly Val
          50           55           60
Ala Ala Lys Asn Gln Gln Ile Thr His Ala Asn Asn Thr Val Ser Asn
65           70           75           80
Phe Lys Arg Phe His Gly Arg Ala Phe Asn Asp Pro Phe Ile Gln Lys
          85           90           95
Glu Lys Glu Asn Leu Ser Tyr Asp Leu Val Pro Leu Lys Asn Gly Gly
          100          105          110
Val Gly Ile Lys Val Met Tyr Met Gly Glu Glu His Leu Phe Ser Val
          115          120          125
Glu Gln Ile Thr Ala Met Leu Leu Thr Lys Leu Lys Glu Thr Ala Glu
          130          135          140
Asn Ser Leu Lys Lys Pro Val Thr Asp Cys Val Ile Ser Val Pro Ser
145          150          155          160
Phe Phe Thr Asp Ala Glu Arg Arg Ser Val Leu Asp Ala Ala Gln Ile
          165          170          175
Val Gly Leu Asn Cys Leu Arg Leu Met Asn Asp Met Thr Ala Val Ala
          180          185          190
Leu Asn Tyr Gly Ile Tyr Lys Gln Asp Leu Pro Ser Leu Asp Glu Lys
          195          200          205
Pro Arg Ile Val Val Phe Val Asp Met Gly His Ser Ala Phe Gln Val
          210          215          220
Ser Ala Cys Ala Phe Asn Lys Gly Lys Leu Lys Val Leu Gly Thr Ala
225          230          235          240
Phe Asp Pro Phe Leu Gly Gly Lys Asn Phe Asp Glu Lys Leu Val Glu
          245          250          255
His Phe Cys Ala Glu Phe Lys Thr Lys Tyr Lys Leu Asp Ala Lys Ser
          260          265          270
Lys Ile Arg Ala Leu Leu Arg Leu Tyr Gln Glu Cys Glu Lys Leu Lys
          275          280          285
Lys Leu Met Ser Ser Asn Ser Thr Asp Leu Pro Leu Asn Ile Glu Cys
          290          295          300
Phe Met Asn Asp Lys Asp Val Ser Gly Lys Met Asn Arg Ser Gln Phe
305          310          315          320
Glu Glu Leu Cys Ala Glu Leu Leu Gln Lys Ile Glu Val Pro Leu Tyr

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-312-

Val Asn Glu Val Met Glu Trp Met Asn Asn Val Met Asn Ala Gln Ala  
 770 775 780  
 Lys Lys Ser Leu Asp Gln Asp Pro Val Val Arg Ala Gln Glu Ile Lys  
 785 790 795 800  
 Thr Lys Ile Lys Glu Leu Asn Asn Thr Cys Glu Pro Val Val Thr Gln  
 805 810 815  
 Pro Lys Pro Lys Ile Glu Ser Pro Lys Leu Glu Arg Thr Pro Asn Gly  
 820 825 830  
 Pro Asn Ile Asp Lys Lys Glu Glu Asp Leu Glu Asp Lys Asn Asn Phe  
 835 840 845  
 Gly Ala Glu Pro Pro His Gln Asn Gly Glu Cys Tyr Pro Asn Glu Lys  
 850 855 860  
 Asn Ser Val Asn Met Asp Leu Asp  
 865 870

<210> 584  
 <211> 2918  
 <212> DNA  
 <213> Homo Sapiens

<400> 584  
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 gctccctgat ggagatggag gggaaggagg atgcccttta aggtgctgaa gtgcatgtac 180  
 tgtggacact cctttgagtc cttgcaggac ctcagcgtcc acatgatcaa aaccaagcat 240  
 taccagaaag tgcctctgaa ggagccagtg ccagccatca ccaaactggt cccctccacc 300  
 aaaaagcggg cgcttcagga cctggcgccc cctgtctccc ctgagccagc aggaatggcc 360  
 gcagaggtgg ccctgagtga gtcagccaag gatcagaaag cagcgaaccc gtacgtcacg 420  
 cccaataacc gctatggcta ccagaatggc gccagctaca cctggcagtt tgaggcccgc 480  
 aaggcgcaga tcctcaagtg catggagtgt ggcagctccc acgacacgct gcagcagctc 540  
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 ggcaagcagt tgggtgctgga ccctgtgggtg gaagagaaga tccagtccat cccactaccg 660  
 cccaccaccc acacgcggct gccggcctcc agcatcaaaa agcagcccga ctctcccgcg 720  
 ggggtccacga cttctgaaga aaagaaagag ccagagaagg agaagccgcc tgtggctggc 780  
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&lt;210&gt; 585

&lt;211&gt; 687

&lt;212&gt; PRT

&lt;213&gt; Homo Sapiens

&lt;400&gt; 585

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Met Ala Ala Glu Val Ala Leu Ser Glu Ser Ala Lys Asp Gln Lys Ala
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Ala Asn Pro Tyr Val Thr Pro Asn Asn Arg Tyr Gly Tyr Gln Asn Gly
20     25     30
Ala Ser Tyr Thr Trp Gln Phe Glu Ala Arg Lys Ala Gln Ile Leu Lys
35     40     45
Cys Met Glu Cys Gly Ser Ser His Asp Thr Leu Gln Gln Leu Thr Ala
50     55     60
His Met Met Val Thr Gly His Phe Leu Lys Val Thr Thr Ser Ala Ser
65     70     75     80
Lys Lys Gly Lys Gln Leu Val Leu Asp Pro Val Val Glu Glu Lys Ile
85     90     95
Gln Ser Ile Pro Leu Pro Pro Thr Thr His Thr Arg Leu Pro Ala Ser
100    105    110
Ser Ile Lys Lys Gln Pro Asp Ser Pro Ala Gly Ser Thr Thr Ser Glu
115    120    125
Glu Lys Lys Glu Pro Glu Lys Glu Lys Pro Pro Val Ala Gly Asp Ala
130    135    140
Glu Lys Ile Lys Glu Glu Ser Glu Asp Ser Leu Glu Lys Phe Glu Pro
145    150    155    160
Ser Thr Leu Tyr Pro Tyr Leu Arg Glu Glu Asp Leu Asp Asp Ser Pro
165    170    175
Lys Gly Gly Leu Asp Ile Leu Lys Ser Leu Glu Asn Thr Val Ser Thr
180    185    190
Ala Ile Ser Lys Ala Gln Asn Gly Ala Pro Ser Trp Gly Gly Tyr Pro
195    200    205
Ser Ile His Ala Ala Tyr Gln Leu Pro Gly Thr Val Lys Pro Leu Pro
210    215    220
Ala Ala Val Gln Ser Val Gln Val Gln Pro Ser Tyr Ala Gly Gly Val
225    230    235    240
Lys Ser Leu Ser Ser Ala Glu His Asn Ala Leu Leu His Ser Pro Gly
245    250    255
Ser Leu Thr Pro Pro Pro His Lys Ser Asn Val Ser Ala Met Glu Glu

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	260		265		270
Leu Val Glu	Lys Val Thr Gly	Lys Val Asn Ile	Lys Lys Glu	Glu Arg	
275		280		285	
Pro Pro Glu	Lys Glu Lys Ser	Leu Ala Lys	Ala Ala Ser	Pro Ile	
290		295		300	
Ala Lys Glu	Asn Lys Asp Phe	Pro Lys Thr	Glu Glu Val	Ser Gly Lys	
305		310		315	320
Pro Gln Lys	Lys Gly Pro Glu	Ala Glu Thr	Trp Glu Ala	Lys Lys Glu	
	325		330		335
Gly Pro Leu	Asp Val His Thr	Pro Asn Gly	Thr Glu Pro	Leu Lys Ala	
	340		345		350
Lys Val Thr	Asn Gly Cys Asn	Asn Leu Gly	Ile Ile Met	Asp His Ser	
	355		360		365
Pro Glu Pro	Ser Phe Ile Asn	Pro Leu Ser	Ala Leu Gln	Ser Ile Met	
	370		375		380
Asn Thr His	Leu Gly Lys Val	Ser Lys Pro	Val Ser Pro	Ser Leu Asp	
385		390		395	400
Pro Leu Ala	Met Leu Tyr Lys	Ile Ser Asn	Ser Met Leu	Asp Lys Pro	
	405		410		415
Val Tyr Pro	Ala Thr Pro Val	Lys Gln Ala	Asp Ala Ile	Asp Arg Tyr	
	420		425		430
Tyr Tyr Glu	Asn Ser Asp Gln	Pro Ile Asp	Leu Thr Lys	Ser Lys Asn	
	435		440		445
Lys Pro Leu	Val Ser Ser Val	Ala Asp Ser	Val Ala Ser	Pro Leu Arg	
	450		455		460
Glu Ser Ala	Leu Met Asp Ile	Ser Asp Met	Val Lys Asn	Leu Thr Gly	
465		470		475	480
Arg Leu Thr	Pro Lys Ser Ser	Thr Pro Ser	Thr Val Ser	Glu Lys Ser	
	485		490		495
Asp Ala Asp	Gly Ser Ser Phe	Glu Glu Ala	Leu Asp Glu	Leu Ser Pro	
	500		505		510
Val His Lys	Arg Lys Gly Arg	Gln Ser Asn	Trp Asn Pro	Gln His Leu	
	515		520		525
Leu Ile Leu	Gln Ala Gln Phe	Ala Ser Ser	Leu Arg Glu	Thr Thr Glu	
	530		535		540
Gly Lys Tyr	Ile Met Ser Asp	Leu Gly Pro	Gln Glu Arg	Val His Ile	
545		550		555	560
Ser Lys Phe	Thr Gly Leu Ser	Met Thr Thr	Ile Ser His	Trp Leu Ala	
	565		570		575
Asn Val Lys	Tyr Gln Leu Arg	Arg Thr Gly	Gly Thr Lys	Phe Leu Lys	
	580		585		590
Asn Leu Asp	Thr Gly His Pro	Val Phe Phe	Cys Asn Asp	Cys Ala Ser	
	595		600		605
Gln Phe Arg	Thr Ala Ser Thr	Tyr Ile Ser	His Leu Glu	Thr His Leu	
	610		615		620
Gly Phe Ser	Leu Lys Asp Leu	Ser Lys Leu	Pro Leu Asn	Gln Ile Gln	
625		630		635	640
Glu Gln Gln	Asn Val Ser Lys	Val Leu Thr	Asn Lys Thr	Leu Gly Pro	
	645		650		655
Leu Gly Ala	Thr Glu Glu Asp	Leu Gly Ser	Thr Phe Gln	Cys Lys Leu	
	660		665		670
Cys Asn Arg	Thr Phe Ala Lys	Gln Ala Arg	Ser Gln Thr	Ala Pro	
	675		680		685

&lt;210&gt; 586

&lt;211&gt; 1898

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 586

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accagccccg ctcanaggtc tgcggggggg acctggccct gccccagtg cctaaggagg      360
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ctcgaggggc cgtgatggag cagggcacgt cctcgtcaat gacagagtcg tctcccagga      480
gtatgctagg ctatgacaga gatggaaggc aggtggcctc agactcccat gtgggtcccca      540
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&lt;210&gt; 587

&lt;211&gt; 399

&lt;212&gt; PRT

&lt;213&gt; Homo Sapiens

&lt;400&gt; 587

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Ala Leu Gly Gln Pro Ala Pro Leu Leu Pro Ala Ala Val Gly Ala Val
 1              5              10              15
Ser Leu Ala Thr Ser Gln Leu Pro Ser Pro Pro Leu Gly Pro Thr Val
 20              25              30
Pro Pro Gln Pro Pro Ser Ala Leu Glu Ser Asp Gly Glu Gly Pro Pro
 35              40              45
Pro Arg Val Gly Phe Val Asp Ser Thr Ile Lys Ser Leu Asp Lys Leu
 50              55              60
Arg Thr Leu Leu Tyr Gln Glu His Val Pro Thr Ser Ser Ala Ser Ala
 65              70              75              80
Gly Thr Pro Val Glu Val Gly Asp Arg Phe Thr Leu Glu Pro Leu Arg

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<210> 588
<211> 707
<212> DNA
<213> Homo Sapiens
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-317-

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aagaattcac	ngtccgagat	ggctacatcc	attatggaca	aacagtc		707

&lt;210&gt; 589

&lt;211&gt; 551

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 589

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atcacctggg	atgaaaagtt	ttcccaagaa	accacaaacg	attgttcatt	ttttctcctt	120
ttttgttaac	tttttgccac	actcaagtca	gtttaagtcc	tagcaaaaag	acggtagtta	180
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ttgccggacc	catctccaac	cttctcggaa	tgcanaaatg	tctgggacga	cacagaacat	480
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ggantnaaaa	t					551

&lt;210&gt; 590

&lt;211&gt; 478

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 590

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&lt;210&gt; 591

&lt;211&gt; 707

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 591

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&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 595

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&lt;210&gt; 596

&lt;211&gt; 835

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 596

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&lt;210&gt; 597

&lt;211&gt; 443

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 597

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&lt;210&gt; 598

&lt;211&gt; 491

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 598

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&lt;211&gt; 802

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 599

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&lt;210&gt; 600

&lt;211&gt; 523

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 600

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&lt;211&gt; 530

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 601

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&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 602

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&lt;210&gt; 603

&lt;211&gt; 289

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 603

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&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 604

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&lt;213&gt; Homo Sapiens

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&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 606

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&lt;210&gt; 607

&lt;211&gt; 687

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 607

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&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

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&lt;210&gt; 609

&lt;211&gt; 843

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 609

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&lt;211&gt; 707

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 610

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&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 614

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&lt;211&gt; 714

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 615

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&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 616

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&lt;211&gt; 753

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 627

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&lt;211&gt; 675

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 628

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698

&lt;210&gt; 632

&lt;211&gt; 466

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 632

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&lt;211&gt; 734

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 633

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&lt;211&gt; 822

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 634

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&lt;211&gt; 619

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 638

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&lt;211&gt; 694

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 639

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&lt;211&gt; 728

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

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&lt;210&gt; 644

&lt;211&gt; 749

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 644

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&lt;210&gt; 645

&lt;211&gt; 751

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 645

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&lt;210&gt; 646

&lt;211&gt; 760

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 646

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&lt;210&gt; 647

&lt;211&gt; 1041

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 647

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&lt;210&gt; 648

&lt;211&gt; 810

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 648

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&lt;210&gt; 649

&lt;211&gt; 656

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 649

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&lt;210&gt; 650

&lt;211&gt; 645

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 650

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&lt;210&gt; 651

&lt;211&gt; 780

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 651

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&lt;210&gt; 652

&lt;211&gt; 518

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 652

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&lt;210&gt; 653

&lt;211&gt; 490

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 653

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&lt;210&gt; 654

&lt;211&gt; 359

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 654

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<211> 816

<212> DNA

<213> Homo Sapiens

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<211> 726

<212> DNA

<213> Homo Sapiens

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&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 661

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&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

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&lt;213&gt; Homo Sapiens

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&lt;213&gt; Homo Sapiens

&lt;400&gt; 664

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&lt;211&gt; 1024

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 665

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&lt;211&gt; 734

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 666

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&lt;211&gt; 592

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 667

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&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

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&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

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&lt;210&gt; 673

&lt;211&gt; 1016

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 673

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&lt;210&gt; 674

&lt;211&gt; 1135

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 674

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&lt;210&gt; 675

&lt;211&gt; 1067

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 675

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&lt;211&gt; 784

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 676

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&lt;210&gt; 677

&lt;211&gt; 1362

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 677

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&lt;211&gt; 1771

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 678

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&lt;210&gt; 679

&lt;211&gt; 1367

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 679

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&lt;210&gt; 680

&lt;211&gt; 2545

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 680

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&lt;210&gt; 681

&lt;211&gt; 1745

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 681

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aaaac						1745

&lt;210&gt; 682

&lt;211&gt; 1745

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 682

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catcgccatc	ggagaggcta	ctcaagatgc	agaagcaact	ctgaggaagg	aatcatgat	300
aaaaaaccat	ccccaaaaacc	ttctggattc	aagtctggac	aacacccttt	aatgggcag	360
cctttaattg	agcaggagaa	gtgcagtgc	aattatgagg	cccaagcaga	gaagaatcaa	420
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aaaac						1745

&lt;210&gt; 683

&lt;211&gt; 3127

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 683

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<210> 684  
 <211> 803  
 <212> PRT  
 <213> Homo Sapiens

<400> 684  
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 Lys Ala Thr Ile Pro Glu Val Lys Asn Ser Glu Asn Ser Ser Ser Arg  
 35 40 45  
 Gln Val Ser Ala Asn Asn Gln Phe Ser Ile Thr Lys Asn Arg Asp Gly  
 50 55 60  
 Arg Glu Asn Arg Arg Arg Asn Ser Lys Ile Gly Asp Asp Asn Glu Asn  
 65 70 75 80  
 Leu Thr Phe Lys Leu Glu Val Asn Glu Leu Ser Gly Lys Leu Asp Asn  
 85 90 95  
 Thr Asn Glu Tyr Asn Ser Asn Asp Gly Lys Lys Leu Pro Gln Gly Glu  
 100 105 110  
 Ser Arg Ser Tyr Glu Val Met Gly Ser Met Glu Glu Thr Leu Cys Asn  
 115 120 125  
 Ile Asp Asp Arg Asp Gly Asn Arg Asn Val His Leu Glu Phe Thr Glu  
 130 135 140  
 Arg Glu Ser Arg Lys Asp Gly Glu Asp Glu Phe Val Lys Glu Met Arg  
 145 150 155 160  
 Glu Glu Arg Lys Phe Gln Lys Leu Lys Asn Lys Glu Glu Val Leu Lys  
 165 170 175  
 Ala Ser Arg Glu Glu Lys Val Leu Met Asp Glu Gly Ala Val Leu Thr  
 180 185 190  
 Leu Ala Ala Asp Leu Ser Ser Ala Thr Leu Asp Ile Ser Lys Gln Trp  
 195 200 205  
 Ser Asn Val Phe Asn Ile Leu Arg Glu Asn Asp Phe Glu Pro Lys Phe  
 210 215 220  
 Leu Cys Glu Val Lys Leu Ala Phe Lys Cys Asp Gly Glu Ile Lys Thr  
 225 230 235 240  
 Phe Ser Asp Leu Gln Ser Leu Arg Lys Phe Ala Ser Gln Lys Ser Ser  
 245 250 255  
 Met Xaa Xaa Leu Leu Xaa Asp Val Leu Pro Gln Lys Glu Glu Ile Asn  
 260 265 270  
 Gln Gly Gly Arg Lys Tyr Gly Ile Gln Glu Lys Arg Asp Lys Thr Leu  
 275 280 285  
 Ile Asp Ser Xaa His Arg Ala Gly Glu Ile Thr Ser Asp Gly Leu Ser  
 290 295 300  
 Phe Leu Phe Leu Lys Glu Val Lys Val Ala Lys Pro Glu Glu Met Lys  
 305 310 315 320  
 Asn Leu Glu Thr Gln Glu Glu Glu Phe Ser Glu Leu Glu Glu Leu Asp  
 325 330 335  
 Glu Glu Ala Ser Gly Met Glu Asp Asp Glu Asp Thr Ser Gly Leu Glu  
 340 345 350  
 Glu Glu Glu Glu Glu Glu Ala Ser Gly Leu Glu Glu Asp Xaa Ser Ser  
 355 360 365  
 Xaa Leu Glu Glu Glu Glu Glu Gln Thr Ser Glu Gln Asp Ser Thr Phe  
 370 375 380  
 Xaa Gly His Thr Leu Val Asp Ala Lys His Glu Val Glu Ile Thr Ser



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385          390          395          400
Xaa Gly Met Glu Thr Phe Ile Asp Ser Val Glu Asp Ser Glu Ser
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Glu Glu Glu Glu Gly Lys Ser Ser Glu Thr Gly Lys Val Lys Thr
          420          425          430
Thr Ser Leu Thr Glu Lys Lys Ala Ser Arg Arg Gln Lys Glu Ile Pro
          435          440          445
Phe Ser Tyr Leu Val Gly Asp Ser Gly Lys Lys Lys Leu Val Lys His
          450          455          460
Gln Val Val His Lys Thr Gln Glu Glu Glu Thr Ala Val Pro Thr
465          470          475          480
Ser Gln Gly Thr Gly Thr Thr Cys Leu Thr Leu Cys Leu Ala Ser Pro
          485          490          495
Ser Lys Ser Leu Glu Met Ser His Asp Glu His Lys Lys His Ser His
          500          505          510
Thr Asn Leu Ser Ile Ser Thr Gly Val Thr Lys Leu Lys Lys Thr Glu
          515          520          525
Glu Lys Lys His Arg Thr Leu His Thr Glu Glu Leu Thr Ser Lys Glu
          530          535          540
Ala Asp Leu Thr Glu Glu Thr Glu Glu Asn Leu Arg Ser Ser Val Ile
545          550          555          560
Asn Ser Ile Arg Glu Ile Lys Glu Glu Ile Gly Asn Leu Lys Ser Ser
          565          570          575
His Ser Gly Val Leu Glu Ile Glu Asn Ser Val Asp Asp Leu Ser Ser
          580          585          590
Arg Met Asp Ile Leu Glu Glu Arg Ile Asp Ser Leu Glu Asp Gln Ile
          595          600          605
Glu Glu Phe Ser Lys Asp Thr Met Gln Met Thr Lys Gln Ile Ile Ser
          610          615          620
Lys Glu Gly Pro Arg Asp Ile Glu Glu Arg Ser Arg Ser Cys Asn Ile
625          630          635          640
Arg Leu Ile Gly Ile Pro Glu Lys Glu Ser Tyr Glu Asn Arg Ala Glu
          645          650          655
Asp Ile Ile Lys Glu Ile Ile Asp Glu Asn Phe Ala Glu Leu Lys Lys
          660          665          670
Gly Ser Ser Leu Glu Ile Val Ser Ala Cys Arg Val Pro Ser Lys Ile
          675          680          685
Asp Glu Lys Arg Leu Thr Pro Arg His Ile Leu Val Lys Phe Trp Asn
          690          695          700
Ser Ser Asp Lys Glu Lys Ile Ile Arg Pro Ser Arg Glu Arg Arg Glu
705          710          715          720
Ile Thr Tyr Gln Gly Thr Arg Ile Arg Leu Thr Ala Asp Leu Ser Leu
          725          730          735
Asp Thr Leu Asp Ala Arg Ser Lys Trp Ser Asn Val Phe Lys Val Leu
          740          745          750
Leu Glu Lys Gly Phe Asn Pro Arg Thr Leu Tyr Pro Ala Lys Met Ala
          755          760          765
Phe Asp Phe Arg Gly Lys Thr Lys Val Phe Leu Ser Ile Glu Glu Phe
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Arg Asp Tyr Val Leu His Met Pro Thr Leu Arg Glu Leu Leu Gly Asn
785          790          795          800
Asn Ile Pro

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&lt;210&gt; 685

<211> 947  
 <212> PRT  
 <213> Homo Sapiens

<400> 685  
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 Gln Tyr Leu Gln Lys Val Val Leu Lys Asp Leu Trp Lys His Ser Phe  
 35 40 45  
 Ser Trp Pro Phe Gln Arg Pro Val Asp Ala Val Lys Leu Lys Leu Pro  
 50 55 60  
 Asp Tyr Tyr Thr Ile Ile Lys Asn Pro Met Asp Leu Asn Thr Ile Lys  
 65 70 75 80  
 Lys Arg Leu Glu Asn Lys Tyr Tyr Ala Lys Ala Ser Glu Cys Ile Glu  
 85 90 95  
 Asp Phe Asn Thr Met Phe Ser Asn Cys Tyr Leu Tyr Asn Lys Pro Gly  
 100 105 110  
 Asp Asp Ile Val Leu Met Ala Gln Ala Leu Glu Lys Leu Phe Met Gln  
 115 120 125  
 Lys Leu Ser Gln Met Pro Gln Glu Glu Gln Val Val Gly Val Lys Glu  
 130 135 140  
 Arg Ile Lys Lys Gly Thr Gln Gln Asn Ile Ala Val Ser Ser Ala Lys  
 145 150 155 160  
 Glu Lys Ser Ser Pro Ser Ala Thr Glu Lys Val Phe Lys Gln Gln Glu  
 165 170 175  
 Ile Pro Ser Val Phe Pro Lys Thr Ser Ile Ser Pro Leu Asn Val Val  
 180 185 190  
 Gln Gly Ala Ser Val Asn Ser Ser Ser Gln Thr Ala Ala Gln Val Thr  
 195 200 205  
 Lys Gly Val Lys Arg Lys Ala Asp Thr Thr Thr Pro Ala Thr Ser Ala  
 210 215 220  
 Val Lys Ala Ser Ser Glu Phe Ser Pro Thr Phe Thr Glu Lys Ser Val  
 225 230 235 240  
 Ala Leu Pro Pro Ile Lys Glu Asn Met Pro Lys Asn Val Leu Pro Asp  
 245 250 255  
 Ser Gln Gln Gln Tyr Asn Val Val Glu Thr Val Lys Val Thr Glu Gln  
 260 265 270  
 Leu Arg His Cys Ser Glu Ile Leu Lys Glu Met Leu Ala Lys Lys His  
 275 280 285  
 Phe Ser Tyr Ala Trp Pro Phe Tyr Asn Pro Val Asp Val Asn Ala Leu  
 290 295 300  
 Gly Leu His Asn Tyr Tyr Asp Val Val Lys Asn Pro Met Asp Leu Gly  
 305 310 315 320  
 Thr Ile Lys Glu Lys Met Asp Asn Gln Glu Tyr Lys Asp Ala Tyr Ser  
 325 330 335  
 Phe Ala Ala Asp Val Arg Leu Met Phe Met Asn Cys Tyr Lys Tyr Asn  
 340 345 350  
 Pro Pro Asp His Glu Val Val Thr Met Ala Arg Met Leu Gln Asp Val  
 355 360 365  
 Phe Glu Thr His Phe Ser Lys Ile Pro Ile Glu Pro Val Glu Ser Met  
 370 375 380  
 Pro Leu Cys Tyr Ile Lys Thr Asp Ile Thr Glu Thr Thr Gly Arg Glu  
 385 390 395 400

Asn Thr Asn Glu Ala Ser Ser Glu Gly Asn Ser Ser Asp Asp Ser Glu  
 405 410 415  
 Asp Glu Arg Val Lys Arg Leu Ala Lys Leu Gln Glu Gln Leu Lys Ala  
 420 425 430  
 Val His Gln Gln Leu Gln Val Leu Ser Gln Val Pro Phe Arg Lys Leu  
 435 440 445  
 Asn Lys Lys Lys Glu Lys Ser Lys Lys Glu Lys Lys Lys Glu Lys Val  
 450 455 460  
 Asn Asn Ser Asn Glu Asn Pro Arg Lys Met Cys Glu Gln Met Arg Leu  
 465 470 475 480  
 Lys Glu Lys Ser Lys Arg Asn Gln Pro Lys Lys Arg Lys Gln Gln Phe  
 485 490 495  
 Ile Gly Leu Lys Ser Glu Asp Glu Asp Asn Ala Lys Pro Met Asn Tyr  
 500 505 510  
 Asp Glu Lys Arg Gln Leu Ser Leu Asn Ile Asn Lys Leu Pro Gly Asp  
 515 520 525  
 Lys Leu Gly Arg Val Val His Ile Ile Gln Ser Arg Glu Pro Ser Leu  
 530 535 540  
 Ser Asn Ser Asn Pro Asp Glu Ile Glu Ile Asp Phe Glu Thr Leu Lys  
 545 550 555 560  
 Ala Ser Thr Leu Arg Glu Leu Glu Lys Tyr Val Ser Ala Cys Leu Arg  
 565 570 575  
 Lys Arg Pro Leu Lys Pro Pro Ala Lys Lys Ile Met Met Ser Lys Glu  
 580 585 590  
 Glu Leu His Ser Gln Lys Lys Gln Glu Leu Glu Lys Arg Leu Leu Asp  
 595 600 605  
 Val Asn Asn Gln Leu Asn Ser Arg Lys Arg Gln Thr Lys Ser Asp Lys  
 610 615 620  
 Thr Gln Pro Ser Lys Ala Val Glu Asn Val Ser Arg Leu Ser Glu Ser  
 625 630 635 640  
 Ser Ser Ser Ser Ser Ser Ser Ser Glu Ser Glu Ser Ser Ser Ser Asp  
 645 650 655  
 Leu Ser Ser Ser Asp Ser Ser Asp Ser Glu Ser Glu Met Phe Pro Lys  
 660 665 670  
 Phe Thr Glu Val Lys Pro Asn Asp Ser Pro Ser Lys Glu His Val Lys  
 675 680 685  
 Lys Met Lys Asn Glu Cys Ile Leu Pro Glu Gly Arg Thr Gly Val Thr  
 690 695 700  
 Gln Ile Gly Tyr Cys Val Gln Asp Thr Thr Ser Ala Asn Thr Thr Leu  
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 Val His Gln Thr Thr Pro Ser His Val Met Pro Pro Asn His His Gln  
 725 730 735  
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 740 745 750  
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 755 760 765  
 Ser Asn Gly Ile Thr Val Met His Pro Ser Gly Asp Ser Asp Thr Thr  
 770 775 780  
 Met Leu Glu Ser Glu Cys Gln Ala Pro Val Gln Lys Asp Ile Lys Ile  
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 Lys Asn Ala Asp Ser Trp Lys Ser Leu Gly Lys Pro Val Lys Pro Ser  
 805 810 815  
 Gly Val Met Lys Ser Ser Asp Glu Leu Phe Asn Gln Phe Arg Lys Ala  
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 Ala Ile Glu Lys Glu Val Lys Ala Arg Thr Gln Glu Leu Ile Arg Lys

835	840	845
His Leu Glu Gln Asn Thr Lys Glu Leu Lys Ala Ser Gln Glu Asn Gln		
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Arg Asp Leu Gly Asn Gly Leu Thr Val Glu Ser Phe Ser Asn Lys Ile		
865	870	875
Gln Asn Lys Cys Ser Gly Glu Glu Gln Lys Glu His Pro Gln Ser Ser		880
885	890	895
Glu Ala Gln Asp Lys Ser Lys Leu Trp Leu Leu Lys Asp Arg Asp Leu		
900	905	910
Ala Arg Pro Lys Glu Gln Glu Arg Arg Arg Arg Glu Ala Met Val Gly		
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Thr Ile Asp Met Thr Leu Gln Ser Asp Ile Met Thr Met Phe Glu Asn		
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Asn Phe Asp		
945		

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 <211> 3106  
 <212> DNA  
 <213> Homo Sapiens

<400> 686

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&lt;210&gt; 687

&lt;211&gt; 1759

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 687

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1759

<210> 688  
 <211> 207  
 <212> PRT  
 <213> Homo Sapiens

<400> 688  
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 35 40 45  
 Thr Glu Ala Leu Ser Val Ser Gln Glu Arg Val Gly Met Ser Leu Val  
 50 55 60  
 Ala Leu Lys Lys Ala Leu Ala Ala Ala Gly Tyr Asp Val Glu Lys Asn  
 65 70 75 80  
 Asn Ser Arg Ile Lys Leu Ser Leu Lys Ser Leu Val Asn Lys Gly Ile  
 85 90 95  
 Leu Val Gln Thr Arg Gly Thr Gly Ala Ser Gly Ser Phe Lys Leu Ser  
 100 105 110  
 Lys Lys Val Ile Pro Lys Ser Thr Arg Ser Lys Ala Lys Lys Ser Val  
 115 120 125  
 Ser Ala Lys Thr Lys Lys Leu Val Leu Ser Arg Asp Ser Lys Ser Pro  
 130 135 140  
 Lys Thr Ala Lys Thr Asn Lys Arg Ala Lys Lys Pro Arg Ala Thr Thr  
 145 150 155 160  
 Pro Lys Thr Val Arg Ser Gly Arg Lys Ala Lys Gly Ala Lys Gly Lys  
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<210> 689  
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 <212> DNA  
 <213> Homo Sapiens

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&lt;210&gt; 690

&lt;211&gt; 363

&lt;212&gt; PRT

&lt;213&gt; Homo Sapiens

&lt;400&gt; 690

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Asp Glu Ser Thr Gly Ser Ile Ala Lys Arg Leu Gln Ser Ile Gly Thr
35 40 45
Glu Asn Thr Glu Glu Asn Arg Arg Phe Tyr Arg Gln Leu Leu Leu Thr
50 55 60
Ala Asp Asp Arg Val Asn Pro Cys Ile Gly Gly Val Ile Leu Phe His
65 70 75 80
Glu Thr Leu Tyr Gln Lys Ala Asp Asp Gly Arg Pro Phe Pro Gln Val
85 90 95
Ile Lys Ser Lys Gly Gly Val Val Gly Ile Lys Val Asp Lys Gly Val
100 105 110
Val Pro Leu Ala Gly Thr Asn Gly Glu Thr Thr Thr Gln Gly Leu Asp
115 120 125
Gly Leu Ser Glu Arg Cys Ala Gln Tyr Lys Lys Asp Gly Ala Asp Phe
130 135 140
Ala Lys Trp Arg Cys Val Leu Lys Ile Gly Glu His Thr Pro Ser Ala
145 150 155 160
Leu Ala Ile Met Glu Asn Ala Asn Val Leu Ala Arg Tyr Ala Ser Ile
165 170 175
Cys Gln Gln Asn Gly Ile Val Pro Ile Val Glu Pro Glu Ile Leu Pro
180 185 190
Asp Gly Asp His Asp Leu Lys Arg Cys Gln Tyr Val Thr Glu Lys Val
195 200 205
Leu Ala Ala Val Tyr Lys Ala Leu Ser Asp His His Ile Tyr Leu Glu
210 215 220
Gly Thr Leu Leu Lys Pro Asn Met Val Thr Pro Gly His Ala Cys Thr
225 230 235 240
Gln Lys Phe Ser His Glu Glu Ile Ala Met Ala Thr Val Thr Ala Leu
245 250 255
Arg Arg Thr Val Pro Pro Ala Val Thr Gly Ile Thr Phe Leu Ser Gly
260 265 270
Gly Gln Ser Glu Glu Glu Ala Ser Ile Asn Leu Asn Ala Ile Asn Lys
275 280 285
Cys Pro Leu Leu Lys Pro Trp Ala Leu Thr Phe Ser Tyr Gly Arg Ala

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290                                      295                                      300  
 Leu Gln Ala Ser Ala Leu Lys Ala Trp Gly Gly Lys Lys Glu Asn Leu  
 305                                      310                                      315                                      320  
 Lys Ala Ala Gln Glu Tyr Val Lys Arg Ala Leu Ala Asn Ser Leu  
                                     325                                      330                                      335  
 Ala Cys Gln Gly Lys Tyr Thr Pro Ser Gly Gln Ala Gly Ala Ala Ala  
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 Ser Glu Ser Leu Phe Val Ser Asn His Ala Tyr  
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<210> 691  
 <211> 1216  
 <212> DNA  
 <213> Homo Sapiens

<400> 691  
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<210> 692  
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 <212> DNA  
 <213> Homo Sapiens

<400> 692  
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&lt;210&gt; 693

&lt;211&gt; 505

&lt;212&gt; PRT

&lt;213&gt; Homo Sapiens

&lt;400&gt; 693

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Ala Pro Gly Gly Gly Pro Trp Gly Gly Ala Ala Tyr Pro Pro Pro Pro
20          25          30
Ser Met Pro Pro Ile Gly Leu Asp Asn Val Ala Thr Tyr Ala Gly Gln
35          40          45
Phe Asn Gln Asp Tyr Leu Ser Gly Met Ala Ala Asn Met Ser Gly Thr
50          55          60
Phe Gly Gly Ala Asn Met Pro Asn Leu Tyr Pro Gly Ala Pro Gly Ala
65          70          75          80
Gly Tyr Pro Pro Val Pro Pro Gly Gly Phe Gly Gln Pro Pro Ser Ala
85          90          95
Gln Gln Pro Val Pro Pro Tyr Gly Met Tyr Pro Pro Pro Gly Gly Asn
100          105          110
Pro Pro Ser Arg Met Pro Ser Tyr Pro Pro Tyr Pro Gly Ala Pro Val
115          120          125
Pro Gly Gln Pro Met Pro Pro Pro Gly Gln Gln Pro Pro Gly Ala Tyr
130          135          140
Pro Gly Gln Pro Pro Val Thr Tyr Pro Gly Gln Pro Pro Val Pro Leu
145          150          155          160
Pro Gly Gln Gln Gln Pro Val Pro Ser Tyr Pro Gly Tyr Pro Gly Ser
165          170          175
Gly Thr Val Thr Pro Ala Val Pro Pro Thr Gln Phe Gly Ser Arg Gly
180          185          190
Thr Ile Thr Asp Ala Pro Gly Phe Asp Pro Leu Arg Asp Ala Glu Val
195          200          205

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Leu Arg Lys Ala Met Lys Gly Phe Gly Thr Asp Glu Gln Ala Ile Ile  
 210 215 220  
 Asp Cys Leu Gly Ser Arg Ser Asn Lys Gln Arg Gln Gln Ile Leu Leu  
 225 230 235 240  
 Ser Phe Lys Thr Ala Tyr Gly Lys Asp Leu Ile Lys Asp Leu Lys Ser  
 245 250 255  
 Glu Leu Ser Gly Asn Phe Glu Lys Thr Ile Leu Ala Leu Met Lys Thr  
 260 265 270  
 Pro Val Leu Phe Asp Ile Tyr Glu Ile Lys Glu Ala Ile Lys Gly Val  
 275 280 285  
 Gly Thr Asp Glu Ala Cys Leu Ile Glu Ile Leu Ala Ser Arg Ser Asn  
 290 295 300  
 Glu His Ile Arg Glu Leu Asn Arg Ala Tyr Lys Ala Glu Phe Lys Lys  
 305 310 315 320  
 Thr Leu Glu Glu Ala Ile Arg Ser Asp Thr Ser Gly His Phe Gln Arg  
 325 330 335  
 Leu Leu Ile Ser Leu Ser Gln Gly Asn Arg Asp Glu Ser Thr Asn Val  
 340 345 350  
 Asp Met Ser Leu Ala Gln Arg Asp Ala Gln Glu Leu Tyr Ala Ala Gly  
 355 360 365  
 Glu Asn Arg Leu Gly Thr Asp Glu Ser Lys Phe Asn Ala Val Leu Cys  
 370 375 380  
 Ser Arg Ser Arg Ala His Leu Val Ala Val Phe Asn Glu Tyr Gln Arg  
 385 390 395 400  
 Met Thr Gly Arg Asp Ile Glu Lys Ser Ile Cys Arg Glu Met Ser Gly  
 405 410 415  
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 Pro Ala Phe Phe Ala Glu Arg Leu Asn Lys Ala Met Arg Gly Ala Gly  
 435 440 445  
 Thr Lys Asp Arg Thr Leu Ile Arg Ile Met Val Ser Arg Ser Glu Thr  
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 Asp Leu Leu Asp Ile Arg Ser Glu Tyr Lys Arg Met Tyr Gly Lys Ser  
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 <212> DNA  
 <213> Homo Sapiens

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 <213> Homo Sapiens

<400> 695

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 35          40          45
Asp Asn Pro Arg Gly Leu Leu Glu Glu Ser Ser Phe Ala Thr Leu Phe
 50          55          60
Pro Lys Tyr Arg Glu Ala Tyr Leu Lys Glu Cys Trp Pro Leu Val Gln
 65          70          75          80
Lys Ala Leu Asn Glu His His Val Asn Ala Thr Leu Asp Leu Ile Glu
 85          90          95
Gly Ser Met Thr Val Cys Thr Thr Lys Lys Thr Phe Asp Pro Tyr Ile
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Ile Ile Arg Ala Arg Asp Leu Ile Lys Leu Leu Ala Arg Ser Val Ser
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<400> 696

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 <212> DNA  
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<400> 697

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 <212> DNA  
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&lt;210&gt; 699

&lt;211&gt; 1427

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 699

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&lt;210&gt; 700

&lt;211&gt; 1967

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 700

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&lt;210&gt; 701

&lt;211&gt; 3423

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 701

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&lt;210&gt; 702

&lt;211&gt; 1106

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 702

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&lt;210&gt; 703

&lt;211&gt; 1095

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 703

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&lt;210&gt; 704

&lt;211&gt; 1968

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 704

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&lt;210&gt; 705

&lt;211&gt; 800

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 705

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&lt;210&gt; 706

&lt;211&gt; 487

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 706

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aaaaaaaa						487

&lt;210&gt; 707

&lt;211&gt; 3599

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 707

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&lt;210&gt; 708

&lt;211&gt; 1123

&lt;212&gt; PRT

&lt;213&gt; Homo Sapiens

&lt;400&gt; 708

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Ser Gln Glu Glu Arg Phe Ala Pro Gly Trp Asn Arg Asp Tyr Pro Pro
          20          25          30
Pro Pro Leu Lys Ser His Ala Gln Glu Arg His Ser Gly Asn Phe Pro
          35          40          45
Gly Arg Asp Ser Leu Pro Phe Asp Phe Gln Gly His Ser Gly Pro Pro
          50          55          60
Phe Ala Asn Val Glu Glu His Ser Phe Ser Tyr Gly Ala Arg Asp Gly
65          70          75          80
Pro His Gly Asp Tyr Arg Gly Gly Glu Gly Pro Gly His Asp Phe Arg
          85          90          95
Gly Gly Asp Phe Ser Ser Ser Asp Phe Gln Ser Arg Asp Ser Ser Gln
          100         105         110
Leu Asp Phe Arg Gly Arg Asp Ile His Ser Gly Asp Phe Arg Asp Arg
          115         120         125
Glu Gly Pro Pro Met Asp Tyr Arg Gly Gly Asp Gly Thr Ser Met Asp
          130         135         140
Tyr Arg Gly Arg Glu Ala Pro His Met Asn Tyr Arg Asp Arg Asp Ala
145         150         155         160
His Ala Val Asp Phe Arg Gly Arg Asp Ala Pro Pro Ser Asp Phe Arg
          165         170         175
Gly Arg Gly Thr Tyr Asp Leu Asp Phe Arg Gly Arg Asp Gly Ser His
          180         185         190
Ala Asp Phe Arg Gly Arg Asp Leu Ser Asp Leu Asp Phe Arg Ala Arg
          195         200         205
Glu Gln Ser Arg Ser Asp Phe Arg Asn Arg Asp Val Ser Asp Leu Asp
          210         215         220
Phe Arg Asp Lys Asp Gly Thr Gln Val Asp Phe Arg Gly Arg Gly Ser
225         230         235         240
Gly Thr Thr Asp Leu Asp Phe Arg Asp Arg Asp Thr Pro His Ser Asp
          245         250         255

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Phe Arg Gly Arg His Arg Ser Arg Thr Asp Gln Asp Phe Arg Gly Arg  
 260 265 270  
 Glu Met Gly Ser Cys Met Glu Phe Lys Asp Arg Glu Met Pro Pro Val  
 275 280 285  
 Asp Pro Asn Ile Leu Asp Tyr Ile Gln Pro Ser Thr Gln Asp Arg Glu  
 290 295 300  
 His Ser Gly Met Asn Val Asn Arg Arg Glu Glu Ser Thr His Asp His  
 305 310 315 320  
 Thr Ile Glu Arg Pro Ala Phe Gly Ile Gln Lys Gly Glu Phe Glu His  
 325 330 335  
 Ser Glu Thr Arg Glu Gly Glu Thr Gln Gly Val Ala Phe Glu His Glu  
 340 345 350  
 Ser Pro Ala Asp Phe Gln Asn Ser Gln Ser Pro Val Gln Asp Gln Asp  
 355 360 365  
 Lys Ser Gln Leu Ser Gly Arg Glu Glu Gln Ser Ser Asp Ala Gly Leu  
 370 375 380  
 Phe Lys Glu Glu Gly Gly Leu Asp Phe Leu Gly Arg Gln Asp Thr Asp  
 385 390 395 400  
 Tyr Arg Ser Met Glu Tyr Arg Asp Val Asp His Arg Leu Pro Gly Ser  
 405 410 415  
 Gln Met Phe Gly Tyr Gly Gln Ser Lys Ser Phe Pro Glu Gly Lys Thr  
 420 425 430  
 Ala Arg Asp Ala Gln Arg Asp Leu Gln Asp Gln Asp Tyr Arg Thr Gly  
 435 440 445  
 Pro Ser Glu Glu Lys Pro Ser Arg Leu Ile Arg Leu Ser Gly Val Pro  
 450 455 460  
 Glu Asp Ala Thr Lys Glu Glu Ile Leu Asn Ala Phe Arg Thr Pro Asp  
 465 470 475 480  
 Gly Met Pro Val Lys Asn Leu Gln Leu Lys Glu Tyr Asn Thr Gly Tyr  
 485 490 495  
 Asp Tyr Gly Tyr Val Cys Val Glu Phe Ser Leu Leu Glu Asp Ala Ile  
 500 505 510  
 Gly Cys Met Glu Ala Asn Gln Gly Thr Leu Met Ile Gln Asp Lys Glu  
 515 520 525  
 Val Thr Leu Glu Tyr Val Ser Ser Leu Asp Phe Trp Tyr Cys Lys Arg  
 530 535 540  
 Cys Lys Ala Asn Ile Gly Gly His Arg Ser Ser Cys Ser Phe Cys Lys  
 545 550 555 560  
 Asn Pro Arg Glu Val Thr Glu Ala Lys Gln Glu Leu Ile Thr Tyr Pro  
 565 570 575  
 Gln Pro Gln Lys Thr Ser Ile Pro Ala Pro Leu Glu Lys Gln Pro Asn  
 580 585 590  
 Gln Pro Leu Arg Pro Ala Asp Lys Glu Pro Glu Pro Arg Lys Arg Glu  
 595 600 605  
 Glu Gly Gln Glu Ser Arg Leu Gly His Gln Lys Arg Glu Ala Glu Arg  
 610 615 620  
 Tyr Leu Pro Pro Ser Arg Arg Glu Gly Pro Thr Phe Arg Arg Asp Arg  
 625 630 635 640  
 Glu Arg Glu Ser Trp Ser Gly Glu Thr Arg Gln Asp Gly Glu Ser Lys  
 645 650 655  
 Thr Ile Met Leu Lys Arg Ile Tyr Arg Ser Thr Pro Pro Glu Val Ile  
 660 665 670  
 Val Glu Val Leu Glu Pro Tyr Val Arg Leu Thr Thr Ala Asn Val Arg  
 675 680 685  
 Ile Ile Lys Asn Arg Thr Gly Pro Met Gly His Thr Tyr Gly Phe Ile

690	695	700
Asp Leu Asp Ser His Val Glu Ala Leu Arg Val Val Lys Ile Leu Gln		
705	710	715
Asn Leu Asp Pro Pro Phe Ser Ile Asp Gly Lys Met Val Ala Val Asn		
	725	730
Leu Ala Thr Gly Lys Arg Arg Asn Asp Ser Gly Asp His Ser Asp His		
	740	745
Met His Tyr Tyr Gln Gly Lys Lys Tyr Phe Arg Asp Arg Arg Gly Gly		
	755	760
Gly Arg Asn Ser Asp Trp Ser Ser Asp Thr Asn Arg Gln Gly Gln Gln		
	770	775
Ser Ser Ser Asp Cys Tyr Ile Tyr Asp Ser Ala Ser Gly Tyr Tyr Tyr		
785	790	795
Asp Pro Leu Ala Gly Thr Tyr Tyr Asp Pro Asn Thr Gln Gln Glu Val		
	805	810
Tyr Val Pro Gln Asp Pro Gly Leu Pro Glu Glu Glu Glu Ile Lys Glu		
	820	825
Lys Lys Pro Thr Ser Gln Gly Lys Ser Ser Ser Lys Lys Glu Met Ser		
	835	840
Lys Arg Asp Gly Lys Glu Lys Lys Asp Arg Gly Val Thr Arg Phe Gln		
	850	855
Glu Asn Ala Ser Glu Gly Lys Ala Pro Ala Glu Asp Val Phe Lys Lys		
865	870	875
Pro Leu Pro Pro Thr Val Lys Lys Glu Glu Ser Pro Pro Pro Pro Lys		
	885	890
Val Val Asn Pro Leu Ile Gly Leu Leu Gly Glu Tyr Gly Gly Asp Ser		
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Asp Tyr Glu Glu Glu Glu Glu Glu Glu Gln Thr Pro Pro Pro Gln Pro		
	915	920
Arg Thr Ala Gln Pro Gln Lys Arg Glu Glu Gln Thr Lys Lys Glu Asn		
	930	935
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&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 712

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&lt;210&gt; 713

&lt;211&gt; 10

&lt;212&gt; PRT

&lt;213&gt; Homo Sapiens

&lt;400&gt; 713

Asn Val Glu Glu Xaa His Ser Phe Ser Tyr

1

5

10

&lt;210&gt; 714

&lt;211&gt; 10

&lt;212&gt; PRT

&lt;213&gt; Homo Sapiens

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&lt;211&gt; 10

&lt;212&gt; PRT

&lt;213&gt; Homo Sapiens

&lt;400&gt; 746

Thr	Glu	Ala	Lys	Gln	Glu	Leu	Ile	Thr	Tyr
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&lt;210&gt; 747

&lt;211&gt; 10

&lt;212&gt; PRT

&lt;213&gt; Homo Sapiens

&lt;400&gt; 747

Val	Glu	Ala	Leu	Arg	Val	Val	Lys	Ile	Leu
1				5					10

&lt;210&gt; 748

&lt;211&gt; 10

&lt;212&gt; PRT

&lt;213&gt; Homo Sapiens

&lt;400&gt; 748

Gly	Glu	Tyr	Gly	Xaa	Gly	Asp	Ser	Asp	Tyr
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&lt;210&gt; 749

&lt;211&gt; 10

&lt;212&gt; PRT

&lt;213&gt; Homo Sapiens

&lt;400&gt; 749

Leu	Glu	Arg	Arg	Glu	Arg	Glu	Gly	Lys	Phe
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&lt;210&gt; 750

&lt;211&gt; 10

&lt;212&gt; PRT

&lt;213&gt; Homo Sapiens

&lt;400&gt; 750

Arg	Gln	Asp	Gly	Glu	Ser	Lys	Thr	Ile	Met
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&lt;211&gt; 10

&lt;212&gt; PRT

<213> Homo Sapiens

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<210> 786  
<211> 10  
<212> PRT  
<213> Homo Sapiens

<400> 786  
Arg Val Met Phe Ala Arg Tyr Lys Glu Leu  
1 5 10

<210> 787  
<211> 10  
<212> PRT  
<213> Homo Sapiens

<400> 787  
Ser Glu Ala Trp Ser Ser Asn Glu Lys Phe  
1 5 10

<210> 788  
<211> 10



&lt;212&gt; PRT

&lt;213&gt; Homo Sapiens

&lt;400&gt; 788

Arg	Glu	Met	Gly	Xaa	Ser	Cys	Met	Glu	Phe
1				5					10

&lt;210&gt; 789

&lt;211&gt; 10

&lt;212&gt; PRT

&lt;213&gt; Homo Sapiens

&lt;400&gt; 789

Glu	Glu	Gln	Ser	Ser	Asp	Ala	Gly	Leu	Phe
1				5					10

&lt;210&gt; 790

&lt;211&gt; 10

&lt;212&gt; PRT

&lt;213&gt; Homo Sapiens

&lt;400&gt; 790

Lys	Glu	Tyr	Asn	Xaa	Thr	Gly	Tyr	Asp	Tyr
1				5					10

&lt;210&gt; 791

&lt;211&gt; 10

&lt;212&gt; PRT

&lt;213&gt; Homo Sapiens

&lt;400&gt; 791

Thr	Glu	Ala	Lys	Gln	Glu	Leu	Ile	Thr	Tyr
1				5					10

&lt;210&gt; 792

&lt;211&gt; 10

&lt;212&gt; PRT

&lt;213&gt; Homo Sapiens

&lt;400&gt; 792

Val	Glu	Ala	Leu	Arg	Val	Val	Lys	Ile	Leu
1				5					10

&lt;210&gt; 793

&lt;211&gt; 10

&lt;212&gt; PRT

&lt;213&gt; Homo Sapiens

&lt;400&gt; 793

Gly	Glu	Tyr	Gly	Xaa	Gly	Asp	Ser	Asp	Tyr
1				5					10

&lt;210&gt; 794

&lt;211&gt; 10

&lt;212&gt; PRT

&lt;213&gt; Homo Sapiens

&lt;400&gt; 794

Leu Glu Arg Arg Glu Arg Glu Gly Lys Phe  
 1 5 10

&lt;210&gt; 795

&lt;211&gt; 10

&lt;212&gt; PRT

&lt;213&gt; Homo Sapiens

&lt;400&gt; 795

Arg Gln Asp Gly Glu Ser Lys Thr Ile Met  
 1 5 10

&lt;210&gt; 796

&lt;211&gt; 10

&lt;212&gt; PRT

&lt;213&gt; Homo Sapiens

&lt;400&gt; 796

Thr Pro Pro Glu Val Ile Val Glu Val Leu  
 1 5 10

&lt;210&gt; 797

&lt;211&gt; 10

&lt;212&gt; PRT

&lt;213&gt; Homo Sapiens

&lt;400&gt; 797

Tyr Gly Phe Ile Asp Leu Asp Ser His Val  
 1 5 10

&lt;210&gt; 798

&lt;211&gt; 10

&lt;212&gt; PRT

&lt;213&gt; Homo Sapiens

&lt;400&gt; 798

Arg Gln Phe Pro Xaa Asn Lys Glu Val Leu  
 1 5 10

&lt;210&gt; 799

&lt;211&gt; 1464

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 799

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&lt;210&gt; 800

&lt;211&gt; 364

&lt;212&gt; PRT

&lt;213&gt; Homo Sapiens

&lt;400&gt; 800

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Met Pro Tyr Gln Tyr Pro Ala Leu Thr Pro Glu Gln Lys Lys Glu Leu
 1          5          10          15
Ser Asp Ile Ala His Arg Ile Val Ala Pro Gly Lys Gly Ile Leu Ala
          20          25          30
Ala Asp Glu Ser Thr Gly Ser Ile Ala Lys Arg Leu Gln Ser Ile Gly
          35          40          45
Thr Glu Asn Thr Glu Glu Asn Arg Arg Phe Tyr Arg Gln Leu Leu Leu
          50          55          60
Thr Ala Asp Asp Arg Val Asn Pro Cys Ile Gly Gly Val Ile Leu Phe
          65          70          75          80
His Glu Thr Leu Tyr Gln Lys Ala Asp Asp Gly Arg Pro Phe Pro Gln
          85          90          95
Val Ile Lys Ser Lys Gly Gly Val Val Gly Ile Lys Val Asp Lys Gly
          100          105          110
Val Val Pro Leu Ala Gly Thr Asn Gly Glu Thr Thr Thr Gln Gly Leu
          115          120          125
Asp Gly Leu Ser Glu Arg Cys Ala Gln Tyr Lys Lys Asp Gly Ala Asp
          130          135          140
Phe Ala Lys Trp Arg Cys Val Leu Lys Ile Gly Glu His Thr Pro Ser
          145          150          155          160
Ala Leu Ala Ile Met Glu Asn Ala Asn Val Leu Ala Arg Tyr Ala Ser
          165          170          175
Ile Cys Gln Gln Asn Gly Ile Val Pro Ile Val Glu Pro Glu Ile Leu
          180          185          190
Pro Asp Gly Asp His Asp Leu Lys Arg Cys Gln Tyr Val Thr Glu Lys
          195          200          205
Val Leu Ala Ala Val Tyr Lys Ala Leu Ser Asp His His Ile Tyr Leu
          210          215          220
Glu Gly Thr Leu Leu Lys Pro Asn Met Val Thr Pro Gly His Ala Cys
          225          230          235          240

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Thr Gln Lys Phe Ser His Glu Glu Ile Ala Met Ala Thr Val Thr Ala  
 245 250 255  
 Leu Arg Arg Thr Val Pro Pro Ala Val Thr Gly Ile Thr Phe Leu Ser  
 260 265 270  
 Gly Gly Gln Ser Glu Glu Glu Ala Ser Ile Asn Leu Asn Ala Ile Asn  
 275 280 285  
 Lys Cys Pro Leu Leu Lys Pro Trp Ala Leu Thr Phe Ser Tyr Gly Arg  
 290 295 300  
 Ala Leu Gln Ala Ser Ala Leu Lys Ala Trp Gly Gly Lys Lys Glu Asn  
 305 310 315 320  
 Leu Lys Ala Ala Gln Glu Glu Tyr Val Lys Arg Ala Leu Ala Asn Ser  
 325 330 335  
 Leu Ala Cys Gln Gly Lys Tyr Thr Pro Ser Gly Gln Ala Gly Ala Ala  
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 Ala Ser Glu Ser Leu Phe Val Ser Asn His Ala Tyr  
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<210> 801  
 <211> 3504  
 <212> DNA  
 <213> Homo Sapiens

<400> 801  
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&lt;210&gt; 802

&lt;211&gt; 429

&lt;212&gt; PRT

&lt;213&gt; Homo Sapiens

&lt;400&gt; 802

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Met Ser Val Asn Val Asn Arg Ser Val Ser Asp Gln Phe Tyr Arg Tyr
1          5          10          15
Lys Met Pro Arg Leu Ile Ala Lys Val Glu Gly Lys Gly Asn Gly Ile
20        25        30
Lys Thr Val Ile Val Asn Met Val Asp Val Ala Lys Ala Leu Asn Arg
35        40        45
Pro Pro Thr Tyr Pro Thr Lys Tyr Phe Gly Cys Glu Leu Gly Ala Gln
50        55        60
Thr Gln Phe Asp Val Lys Asn Asp Arg Tyr Ile Val Asn Gly Ser His
65        70        75        80
Glu Ala Asn Lys Leu Gln Asp Met Leu Asp Gly Phe Ile Lys Lys Phe
85        90        95
Val Leu Cys Pro Glu Cys Glu Asn Pro Glu Thr Asp Leu His Val Asn
100       105       110
Pro Lys Lys Gln Thr Ile Gly Asn Ser Cys Lys Ala Cys Gly Tyr Arg
115       120       125
Gly Met Leu Asp Thr His His Lys Leu Cys Thr Phe Ile Leu Lys Asn
130       135       140
Pro Pro Glu Asn Ser Asp Ile Gly Thr Gly Lys Lys Glu Lys Glu Lys
145       150       155       160
Lys Asn Arg Lys Gly Lys Asp Lys Glu Asn Gly Ser Val Ser Thr Ser

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165 170 175  
 Glu Thr Pro Pro Pro Pro Pro Asn Glu Ile Ser Pro Pro His Ala  
 180 185 190  
 Val Glu Glu Glu Asp Asp Asp Trp Gly Glu Asp Thr Thr Glu Glu  
 195 200 205  
 Ala Gln Arg Arg Arg Met Asp Glu Ile Ser Asp His Ala Lys Gly Leu  
 210 215 220  
 Thr Leu Ser Asp Asp Leu Glu Arg Thr Val Glu Glu Arg Val Asn Ile  
 225 230 235 240  
 Leu Phe Asp Phe Val Lys Lys Lys Lys Glu Glu Gly Ile Ile Asp Ser  
 245 250 255  
 Ser Asp Lys Asp Ile Val Ala Glu Ala Glu Arg Leu Asp Val Lys Ala  
 260 265 270  
 Met Gly Pro Leu Val Leu Thr Glu Val Leu Phe Asp Glu Lys Ile Arg  
 275 280 285  
 Glu Gln Ile Lys Lys Tyr Arg Arg His Phe Leu Arg Phe Cys His Asn  
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 Asn Lys Lys Ala Gln Arg Tyr Leu Leu His Gly Leu Glu Cys Val Val  
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 Ala Met His Gln Ala Gln Leu Ile Ser Lys Ile Pro His Ile Leu Lys  
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 Glu Met Tyr Asp Ala Asp Leu Leu Glu Glu Val Ile Ile Ser Trp  
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 Ser Glu Lys Ala Ser Lys Lys Tyr Val Ser Lys Glu Leu Ala Lys Glu  
 355 360 365  
 Ile Arg Val Lys Ala Glu Pro Phe Ile Lys Trp Leu Lys Glu Ala Glu  
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 Glu Glu Ser Ser Gly Gly Glu Glu Glu Asp Glu Asp Glu Asn Ile Glu  
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<210> 803  
 <211> 2251  
 <212> DNA  
 <213> Homo Sapiens

<400> 803  
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&lt;210&gt; 804

&lt;211&gt; 609

&lt;212&gt; PRT

&lt;213&gt; Homo Sapiens

&lt;400&gt; 804

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Met Lys Trp Val Thr Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
 1             5             10             15
Tyr Ser Arg Gly Val Phe Arg Arg Asp Ala His Lys Ser Glu Val Ala
      20             25             30
His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu
      35             40             45
Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val
      50             55             60
Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp
      65             70             75             80
Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp
      85             90             95
Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala
      100             105             110
Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln
      115             120             125
His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val
      130             135             140
Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys
      145             150             155             160
Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro
      165             170             175
Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys
      180             185             190
Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu

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Leu Arg Asp Glu Gly Lys	Ala Ser Ser Ala Lys	Gln Arg Leu Lys Cys
210	215	220
Ala Ser Leu Gln Lys Phe	Gly Glu Arg Ala Phe	Lys Ala Trp Ala Val
225	230	235
Ala Arg Leu Ser Gln Arg	Phe Pro Lys Ala Glu	Phe Ala Glu Val Ser
245	250	255
Lys Leu Val Thr Asp Leu	Thr Lys Val His Thr	Glu Cys Cys His Gly
260	265	270
Asp Leu Leu Glu Cys Ala	Asp Asp Arg Ala Asp	Leu Ala Lys Tyr Ile
275	280	285
Cys Glu Asn Gln Asp Ser	Ile Ser Ser Lys Leu	Lys Glu Cys Cys Glu
290	295	300
Lys Pro Leu Leu Glu Lys	Ser His Cys Ile Ala	Glu Val Glu Asn Asp
305	310	315
Glu Met Pro Ala Asp Leu	Pro Ser Leu Ala Ala	Asp Phe Val Glu Ser
325	330	335
Lys Asp Val Cys Lys Asn	Tyr Ala Glu Ala Lys	Asp Val Phe Leu Gly
340	345	350
Met Phe Leu Tyr Glu Tyr	Ala Arg Arg His Pro	Asp Tyr Ser Val Val
355	360	365
Leu Leu Leu Arg Leu Ala	Lys Thr Tyr Glu Thr	Thr Leu Glu Lys Cys
370	375	380
Cys Ala Ala Ala Asp Pro	His Glu Cys Tyr Ala	Lys Val Phe Asp Glu
385	390	395
Phe Lys Pro Leu Val Glu	Glu Glu Pro Gln Asn	Leu Ile Lys Gln Asn Cys
405	410	415
Glu Leu Phe Lys Gln Leu	Gly Glu Tyr Lys Phe	Gln Asn Ala Leu Leu
420	425	430
Val Arg Tyr Thr Lys Lys	Val Pro Gln Val Ser	Thr Pro Thr Leu Val
435	440	445
Glu Val Ser Arg Asn Leu	Gly Lys Val Gly Ser	Lys Cys Cys Lys His
450	455	460
Pro Glu Ala Lys Arg Met	Pro Cys Ala Glu Asp	Tyr Leu Ser Val Val
465	470	475
Leu Asn Gln Leu Cys Val	Leu His Glu Lys Thr	Pro Val Ser Asp Arg
485	490	495
Val Thr Lys Cys Cys Thr	Glu Ser Leu Val Asn	Arg Arg Pro Cys Phe
500	505	510
Ser Ala Leu Glu Val Asp	Glu Thr Tyr Val Pro	Lys Glu Phe Asn Ala
515	520	525
Glu Thr Phe Thr Phe His	Ala Asp Ile Cys Thr	Leu Ser Glu Lys Glu
530	535	540
Arg Gln Ile Lys Lys Gln	Thr Ala Leu Val Glu	Leu Val Lys His Lys
545	550	555
Pro Lys Ala Thr Lys Glu	Gln Leu Lys Ala Val	Met Asp Asp Phe Ala
565	570	575
Ala Phe Val Glu Lys Cys	Cys Lys Ala Asp Asp	Lys Glu Thr Cys Phe
580	585	590
Ala Glu Glu Gly Lys Lys	Leu Val Ala Ala Ser	Gln Ala Ala Leu Gly
595	600	605
Leu		

&lt;210&gt; 805



<211> 1356  
 <212> DNA  
 <213> Homo Sapiens

<400> 805  
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 ctctttgtag acattcctgc aaaaaagggtt tgccggtggg attcattcac caagcaagta 240  
 cagcgagtga ccatggatgc cccagtcagc tccgtggctc ttcgccagtc gggaggctat 300  
 gttgccacca ttggaacaaa gttctgtgct ttgaactgga aagaacaatc agcagttgtc 360  
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 gccgggaggt actttgctgg caccatggct gaggaacag ctccagcagt tcttgagcgg 480  
 caccaggggg ccctgtactc cctcttttct gatcaccacg tgaaaaagta ctttgaccag 540  
 gtggacattt ccaatggttt ggattggctg ctagaccaca aaatcttcta ttacattgac 600  
 agcctgtcct actccgtgga tgcctttgac tatgacctgc agacaggaca gatctccaac 660  
 cgcagaagtg ttacaagct agaaaaggaa gaacaaatcc cagatggaat gtgtattgat 720  
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 atttttaaca aggggtgaca ggtggttttg ataacacact tataaggctt tctgtaaaag 1200  
 gtactataga agggcgaaga atcgttcaac tgtcaatcag cctcttgatt ctttgtaaag 1260  
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 aagcttcaag gaacaataaa tagtaacctg gtaatg 1356

<210> 806  
 <211> 299  
 <212> PRT  
 <213> Homo Sapiens

<400> 806  
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 1 5 10 15  
 Gly Glu Ser Pro Val Trp Glu Glu Val Ser Asn Ser Leu Leu Phe Val  
 20 25 30  
 Asp Ile Pro Ala Lys Lys Val Cys Arg Trp Asp Ser Phe Thr Lys Gln  
 35 40 45  
 Val Gln Arg Val Thr Met Asp Ala Pro Val Ser Ser Val Ala Leu Arg  
 50 55 60  
 Gln Ser Gly Gly Tyr Val Ala Thr Ile Gly Thr Lys Phe Cys Ala Leu  
 65 70 75 80  
 Asn Trp Lys Glu Gln Ser Ala Val Val Leu Ala Thr Val Asp Asn Asp  
 85 90 95  
 Lys Lys Asn Asn Arg Phe Asn Asp Gly Lys Val Asp Pro Ala Gly Arg  
 100 105 110  
 Tyr Phe Ala Gly Thr Met Ala Glu Glu Thr Ala Pro Ala Val Leu Glu  
 115 120 125  
 Arg His Gln Gly Ala Leu Tyr Ser Leu Phe Pro Asp His His Val Lys  
 130 135 140  
 Lys Tyr Phe Asp Gln Val Asp Ile Ser Asn Gly Leu Asp Trp Ser Leu  
 145 150 155 160

Asp His Lys Ile Phe Tyr Tyr Ile Asp Ser Leu Ser Tyr Ser Val Asp  
 165 170 175  
 Ala Phe Asp Tyr Asp Leu Gln Thr Gly Gln Ile Ser Asn Arg Arg Ser  
 180 185 190  
 Val Tyr Lys Leu Glu Lys Glu Glu Gln Ile Pro Asp Gly Met Cys Ile  
 195 200 205  
 Asp Ala Glu Gly Lys Leu Trp Val Ala Cys Tyr Asn Gly Gly Arg Val  
 210 215 220  
 Ile Arg Leu Asp Pro Val Thr Gly Lys Arg Leu Gln Thr Val Lys Leu  
 225 230 235 240  
 Pro Val Asp Lys Thr Thr Ser Cys Cys Phe Gly Gly Lys Asn Tyr Ser  
 245 250 255  
 Glu Met Tyr Val Thr Cys Ala Arg Asp Gly Met Asp Pro Glu Gly Leu  
 260 265 270  
 Leu Arg Gln Pro Glu Ala Gly Gly Ile Phe Lys Ile Thr Gly Leu Gly  
 275 280 285  
 Val Lys Gly Ile Ala Pro Tyr Ser Tyr Ala Gly  
 290 295

&lt;210&gt; 807

&lt;211&gt; 1980

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 807

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atcaatccag gcaaaactaga tgtggaaggc agatctgcct tccatgttgt ggccctcaaag      240
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ttacttaaaa atggtgctga tgtaagcctg ctggatgcct tgggccatga tagttcttac      720
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tacatgctag atgaagtaaa tgtgaagtca agtcagaggg agcatcgaaa cattcaggag      900
ctggagattg aaaatgaaga ttgaaagac aggttgagaa aaattcagca agaacagaga      960
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gatgatctgg aaagtgagaa agaaaagctg aagtctcttt tgggtggctaa agaaaagcaa      1080
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caaaatgagc tgctagtaga acagtttagg agagatgaag gcaagctggt ggaagagaat      1680
aagcgattgc agaaggaact cagtatgtgt gaaacggatt gagacaagaa aggaaggagg      1740
gttgctgagg tggaaggcca ggtaaaggaa ctcttaggaa agctgacctt gtcagttcca      1800

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actgaaaaat ttgagagcat gaagagctta ttatcaagcg aagtaaatga gaagggtgaaa 1860  
 aaaattggag agacagaaaag agagtatgaa aaatcactta ctgaaatcag acagttaagg 1920  
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<210> 808

<211> 659

<212> PRT

<213> Homo Sapiens

<400> 808

Met	Pro	Ser	Ser	Leu	Leu	Leu	Ala	Thr	Arg	Asn	Gln	Ile	Leu	Ser	Met
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Met	Asn	Cys	Trp	Phe	Ser	Cys	Ala	Pro	Lys	Asn	Arg	His	Ala	Ala	Asp
			20					25					30		
Trp	Asn	Lys	Tyr	Asp	Asp	Arg	Leu	Met	Lys	Ala	Ala	Glu	Arg	Gly	Asp
			35				40					45			
Val	Glu	Lys	Val	Ser	Ser	Ile	Leu	Ala	Lys	Lys	Gly	Ile	Asn	Pro	Gly
			50			55					60				
Lys	Leu	Asp	Val	Glu	Gly	Arg	Ser	Ala	Phe	His	Val	Val	Ala	Ser	Lys
65					70				75					80	
Gly	Asn	Leu	Glu	Cys	Leu	Asn	Ala	Ile	Leu	Ile	His	Gly	Val	Asp	Ile
				85					90					95	
Thr	Thr	Ser	Asp	Thr	Ala	Gly	Arg	Asn	Ala	Leu	His	Leu	Ala	Ala	Lys
			100					105					110		
Tyr	Gly	His	Ala	Leu	Cys	Leu	Gln	Lys	Leu	Leu	Gln	Tyr	Asn	Cys	Pro
			115				120					125			
Thr	Glu	His	Ala	Asp	Leu	Gln	Gly	Arg	Thr	Ala	Leu	His	Asp	Ala	Ala
			130				135				140				
Met	Ala	Asp	Cys	Pro	Ser	Ser	Ile	Gln	Leu	Leu	Cys	Asp	His	Gly	Ala
145					150				155					160	
Ser	Val	Asn	Ala	Lys	Asp	Val	Asp	Gly	Arg	Thr	Pro	Leu	Val	Leu	Ala
				165					170					175	
Thr	Gln	Met	Cys	Arg	Pro	Ala	Ile	Cys	Gln	Leu	Leu	Ile	Asp	Arg	Gly
			180					185					190		
Ala	Glu	Ile	Asn	Ser	Arg	Asp	Lys	Gln	Asn	Arg	Thr	Ala	Leu	Met	Leu
			195				200					205			
Gly	Cys	Glu	Tyr	Gly	Cys	Lys	Asp	Ala	Val	Glu	Val	Leu	Leu	Lys	Asn
			210			215					220				
Gly	Ala	Asp	Val	Ser	Leu	Leu	Asp	Ala	Leu	Gly	His	Asp	Ser	Ser	Tyr
225					230				235					240	
Tyr	Ala	Arg	Ile	Gly	Asp	Asn	Leu	Asp	Ile	Leu	Thr	Leu	Leu	Lys	Thr
				245					250					255	
Ala	Ser	Glu	Asn	Thr	Asn	Lys	Gly	Arg	Glu	Leu	Trp	Lys	Lys	Gly	Pro
			260					265					270		
Ser	Leu	Gln	Gln	Arg	Asn	Leu	Pro	Tyr	Met	Leu	Asp	Glu	Val	Asn	Val
			275				280					285			
Lys	Ser	Ser	Gln	Arg	Glu	His	Arg	Asn	Ile	Gln	Glu	Leu	Glu	Ile	Glu
			290			295					300				
Asn	Glu	Asp	Leu	Lys	Asp	Arg	Leu	Arg	Lys	Ile	Gln	Gln	Glu	Gln	Arg
305					310				315					320	
Ile	Leu	Leu	Asp	Lys	Val	Asn	Gly	Leu	Gln	Leu	Gln	Leu	Asn	Glu	Glu
				325					330					335	
Val	Met	Val	Ala	Asp	Asp	Leu	Glu	Ser	Glu	Lys	Glu	Lys	Leu	Lys	Ser
			340					345					350		
Leu	Leu	Val	Ala	Lys	Glu	Lys	Gln	His	Glu	Glu	Ser	Leu	Arg	Thr	Ile

355 360 365  
 Glu Ser Leu Lys Asn Arg Phe Lys Tyr Phe Glu Cys Thr Ser Pro Gly  
 370 375 380  
 Val Pro Ala His Met Gln Ser Arg Ser Met Leu Arg Pro Leu Glu Leu  
 385 390 395 400  
 Ser Leu Pro Asn Gln Thr Ser Tyr Ser Glu Asn Asp Leu Leu Lys Lys  
 405 410 415  
 Glu Leu Glu Ala Met Arg Thr Phe Cys Glu Ser Ala Lys Gln Asp Arg  
 420 425 430  
 Leu Lys Leu Gln Asn Gly Val Ala His Lys Val Ala Glu Cys Lys Ala  
 435 440 445  
 Leu Gly Leu Glu Cys Glu Arg Ile Lys Glu Asp Ser Asp Glu Gln Ile  
 450 455 460  
 Lys Gln Leu Glu Asp Ala Leu Lys Asp Val Gln Lys Arg Met Tyr Glu  
 465 470 475 480  
 Ser Glu Gly Lys Val Lys Gln Met Gln Thr His Phe Leu Ala Leu Lys  
 485 490 495  
 Glu His Leu Thr Ser Glu Ala Ala Ile Gly Asn His Arg Leu Met Glu  
 500 505 510  
 Glu Leu Lys Asp Gln Leu Lys Asp Met Lys Ala Lys Tyr Glu Gly Ala  
 515 520 525  
 Ser Ala Glu Val Gly Lys Leu Arg Asn Gln Ile Lys Gln Asn Glu Leu  
 530 535 540  
 Leu Val Glu Gln Phe Arg Arg Asp Glu Gly Lys Leu Val Glu Glu Asn  
 545 550 555 560  
 Lys Arg Leu Gln Lys Glu Leu Ser Met Cys Glu Thr Glu Arg Asp Lys  
 565 570 575  
 Lys Gly Arg Arg Val Ala Glu Val Glu Gly Gln Val Lys Glu Leu Leu  
 580 585 590  
 Ala Lys Leu Thr Leu Ser Val Pro Thr Glu Lys Phe Glu Ser Met Lys  
 595 600 605  
 Ser Leu Leu Ser Ser Glu Val Asn Glu Lys Val Lys Lys Ile Gly Glu  
 610 615 620  
 Thr Glu Arg Glu Tyr Glu Lys Ser Leu Thr Glu Ile Arg Gln Leu Arg  
 625 630 635 640  
 Arg Glu Leu Glu Asn Cys Lys Arg Gln Thr Ser Ser Ala Cys Gln Ala  
 645 650 655  
 Arg Gly Ala

&lt;210&gt; 809

&lt;211&gt; 1725

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 809

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ggccacagag ggcgcggaga gatggccttc agcgggtccc aggcctcccta cctgagtcca	120
gctgtccctt tttctgggac tattcaagga ggtctccagg acggacttca gatcactgtc	180
aatgggaccg ttctcagctc cagtggaaacc aggtttgctg tgaactttca gactggcttc	240
agtggaaatg acattgcctt ccacttcaac cctcggtttg aagatggagg gtacgtgggtg	300
tgcaacacga ggcagaacgg aagctggggg cccgaggaga ggaagacaca catgcctttc	360
cagaaggggg tgccctttga cctctgcttc ctggtgcaga gctcagattt caaggtgatg	420
gtgaacggga tctcttctgt gcagtacttc caccgcgtgc ccttcaccg tgtggacacc	480
atctccgtca atggctctgt gcagctgtcc tacatcagct tccagaaccc ccgcacagtc	540

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cctgttcagc ctgccttctc cacggtgccg ttctcccagc ctgtctgttt cccacccagg 600
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cagacagtca tccacacagt gcagagcgcc cctggacaga tgttctctac tcccgccatc 720
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&lt;210&gt; 810

&lt;211&gt; 355

&lt;212&gt; PRT

&lt;213&gt; Homo Sapiens

&lt;400&gt; 810

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Met Ala Phe Ser Gly Ser Gln Ala Pro Tyr Leu Ser Pro Ala Val Pro
1          5          10          15
Phe Ser Gly Thr Ile Gln Gly Gly Leu Gln Asp Gly Leu Gln Ile Thr
20          25          30
Val Asn Gly Thr Val Leu Ser Ser Ser Gly Thr Arg Phe Ala Val Asn
35          40          45
Phe Gln Thr Gly Phe Ser Gly Asn Asp Ile Ala Phe His Phe Asn Pro
50          55          60
Arg Phe Glu Asp Gly Gly Tyr Val Val Cys Asn Thr Arg Gln Asn Gly
65          70          75          80
Ser Trp Gly Pro Glu Arg Lys Thr His Met Pro Phe Gln Lys Gly
85          90          95
Met Pro Phe Asp Leu Cys Phe Leu Val Gln Ser Ser Asp Phe Lys Val
100          105          110
Met Val Asn Gly Ile Leu Phe Val Gln Tyr Phe His Arg Val Pro Phe
115          120          125
His Arg Val Asp Thr Ile Ser Val Asn Gly Ser Val Gln Leu Ser Tyr
130          135          140
Ile Ser Phe Gln Asn Pro Arg Thr Val Pro Val Gln Pro Ala Phe Ser
145          150          155          160
Thr Val Pro Phe Ser Gln Pro Val Cys Phe Pro Pro Arg Pro Arg Gly
165          170          175
Arg Arg Gln Lys Pro Pro Gly Val Trp Pro Ala Asn Pro Ala Pro Ile
180          185          190
Thr Gln Thr Val Ile His Thr Val Gln Ser Ala Pro Gly Gln Met Phe
195          200          205
Ser Thr Pro Ala Ile Pro Pro Met Met Tyr Pro His Pro Ala Tyr Pro
210          215          220

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Met Pro Phe Ile Thr Thr Ile Leu Gly Gly Leu Tyr Pro Ser Lys Ser
225                230                235                240
Ile Leu Leu Ser Gly Thr Val Leu Pro Ser Ala Gln Arg Phe His Ile
                245                250                255
Asn Leu Cys Ser Gly Asn His Ile Ala Phe His Leu Asn Pro Arg Phe
                260                265                270
Asp Glu Asn Ala Val Val Arg Asn Thr Gln Ile Asp Asn Ser Trp Gly
                275                280                285
Ser Glu Glu Arg Ser Leu Pro Arg Lys Met Pro Phe Val Arg Gly Gln
                290                295                300
Ser Phe Ser Val Trp Ile Leu Cys Glu Ala His Cys Leu Lys Val Ala
305                310                315                320
Val Asp Gly Gln His Leu Phe Glu Tyr Tyr His Arg Leu Arg Asn Leu
                325                330                335
Pro Thr Ile Asn Arg Leu Glu Val Gly Gly Asp Ile Gln Leu Thr His
                340                345                350
Val Gln Thr
                355

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<210> 811
<211> 1022
<212> DNA
<213> Homo Sapiens

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<400> 811
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aagaagaggg cctgggcctg gtgggtgcac aggtcctac tactgaggag caggaggctg      180
ctgtctcttc ctctctctct ctggtcctgg gcaccctgga gaaagtgcct gctgctgagt      240
cagcagatcc tccccagagt cctcagggag cctctgcctt acccactacc atcagcttca      300
cttgctggag gcaacccaat gaggggtcca gcagccaaga agaggaggag gccagcacct      360
cgctgacgc agagtccttg ttccgagaag cactcagtaa caaggtggat gagttggctc      420
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gagtcaccaa aaattacaag cgctgctttc ctgtgatctt cggcaaagcc tccgagtccc      540
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tggctgaaac cagctatgtg aaagtcctgg agcatgtggt caggggtcaat gcaagagttc      960
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ca                                           1022

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<210> 812
<211> 317
<212> PRT
<213> Homo Sapiens

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<400> 812
Met Ser Leu Glu Gln Lys Ser Gln His Cys Lys Pro Glu Glu Gly Val
1          5          10          15
Glu Ala Gln Glu Glu Ala Leu Gly Leu Val Gly Ala Gln Ala Pro Thr
20          25          30
Thr Glu Glu Gln Glu Ala Ala Val Ser Ser Ser Ser Pro Leu Val Leu

```

35	40	45
Gly Thr Leu Glu Lys Val Pro Ala Ala Glu Ser Ala Asp Pro Pro Gln		
50	55	60
Ser Pro Gln Gly Ala Ser Ala Leu Pro Thr Thr Ile Ser Phe Thr Cys		
65	70	75
Trp Arg Gln Pro Asn Glu Gly Ser Ser Ser Gln Glu Glu Glu Glu Ala		
85	90	95
Ser Thr Ser Pro Asp Ala Glu Ser Leu Phe Arg Glu Ala Leu Ser Asn		
100	105	110
Lys Val Asp Glu Leu Ala His Phe Leu Leu Arg Lys Tyr Arg Ala Lys		
115	120	125
Glu Leu Val Thr Lys Ala Glu Met Leu Glu Arg Val Ile Lys Asn Tyr		
130	135	140
Lys Arg Cys Phe Pro Val Ile Phe Gly Lys Ala Ser Glu Ser Leu Lys		
145	150	155
Met Ile Phe Gly Ile Asp Val Lys Glu Val Asp Pro Ala Ser Asn Thr		
165	170	175
Tyr Thr Leu Val Thr Cys Leu Gly Leu Ser Tyr Asp Gly Leu Leu Gly		
180	185	190
Asn Asn Gln Ile Phe Pro Lys Thr Gly Leu Leu Ile Ile Val Leu Gly		
195	200	205
Thr Ile Ala Met Glu Gly Asp Ser Ala Ser Glu Glu Ile Trp Glu		
210	215	220
Glu Leu Gly Val Met Gly Val Tyr Asp Gly Arg Glu His Thr Val Tyr		
225	230	235
Gly Glu Pro Arg Lys Leu Leu Thr Gln Asp Trp Val Gln Glu Asn Tyr		
245	250	255
Leu Glu Tyr Arg Gln Val Pro Gly Ser Asn Pro Ala Arg Tyr Glu Phe		
260	265	270
Leu Trp Gly Pro Arg Ala Leu Ala Glu Thr Ser Tyr Val Lys Val Leu		
275	280	285
Glu His Val Val Arg Val Asn Ala Arg Val Arg Ile Ala Tyr Pro Ser		
290	295	300
Leu Arg Glu Ala Ala Leu Leu Glu Glu Glu Glu Gly Val		
305	310	315

&lt;210&gt; 813

&lt;211&gt; 5175

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 813

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aggcaaagga gaaacagctc tgacatacaa agaaaatgag tatgctaaag ccaagtgggc	180
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&lt;210&gt; 814

&lt;211&gt; 1392

&lt;212&gt; PRT

&lt;213&gt; Homo Sapiens

&lt;400&gt; 814

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&lt;210&gt; 815

&lt;211&gt; 647

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 815

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PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION  
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## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification <sup>6</sup> : <b>G01N 33/574</b>		<b>A2</b>	(11) International Publication Number: <b>WO 99/04265</b>																											
			(43) International Publication Date: 28 January 1999 (28.01.99)																											
(21) International Application Number: <b>PCT/US98/14679</b>		<p>[UA/GB]; 91 Riding House Street, London W1P 8BT (GB). O'HARE, Michael [GB/GB]; 91 Riding House Street, London W1P 8BT (GB). OBATA, Yuichi [JP/JP]; Chikusa-Ku, Nagoya 464 (JP). PFREUNDSCHUH, Michael [DE/DE]; Innere Medizin 1, D-66421 Homburg/Saar (DE). TURECI, Ozlem [DE/DE]; Innere Medizin 1, D-66421 Homburg/Saar (DE). SAHIN, Ugur [TR/DE]; Innere Medizin 1, D-66421 Homburg/Saar (DE).</p> <p>(74) Agent: VAN AMSTERDAM, John, R.; Wolf, Greenfield &amp; Sacks, P.C., 600 Atlantic Avenue, Boston, MA 02210 (US).</p> <p>(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).</p> <p><b>Published</b> Without international search report and to be republished upon receipt of that report.</p>																												
(22) International Filing Date: 15 July 1998 (15.07.98)																														
(30) Priority Data:																														
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9721697.2	11 October 1997 (11.10.97)	GB																												
09/102,322	22 June 1998 (22.06.98)	US																												
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\*(Referred to in PCT Gazette No. 19/1999, Section II)

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PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION  
International Bureau

## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification <sup>6</sup> :

G01N 33/574

A2

(11) International Publication Number:

WO 99/04265

(43) International Publication Date:

28 January 1999 (28.01.99)

(21) International Application Number: PCT/US98/14679

(22) International Filing Date: 15 July 1998 (15.07.98)

## (30) Priority Data:

08/896,164	17 July 1997 (17.07.97)	US
60/061,599	10 October 1997 (10.10.97)	US
60/061,765	10 October 1997 (10.10.97)	US
08/948,705	10 October 1997 (10.10.97)	US
9721697.2	11 October 1997 (11.10.97)	GB
09/102,322	22 June 1998 (22.06.98)	US

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(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

## Published

Without international search report and to be republished upon receipt of that report.

(54) Title: CANCER ASSOCIATED NUCLEIC ACIDS AND POLYPEPTIDES

NY-LU-12 KEESPVPKVVNPLIGLLCEYGGDSYEEEEEEQTTPPPQRTAQPQKREEQTKKENEEDKLTWNKLACLLCRRQFPNKEVL 970  
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## **CANCER ASSOCIATED NUCLEIC ACIDS AND POLYPEPTIDES**

### **Field of the Invention**

The invention relates to nucleic acids and encoded polypeptides which are cancer  
5 associated antigens expressed in patients afflicted with breast cancer. The invention also relates  
to agents which bind the nucleic acids or polypeptides. The nucleic acid molecules,  
polypeptides coded for by such molecules and peptides derived therefrom, as well as related  
antibodies and cytolytic T lymphocytes, are useful, *inter alia*, in diagnostic and therapeutic  
contexts.

10

### **Background of the Invention**

The mechanism by which T cells recognize foreign materials has been implicated in  
cancer. A number of cytolytic T lymphocyte (CTL) clones directed against autologous  
melanoma antigens, testicular antigens, and melanocyte differentiation antigens have been  
15 described. In many instances, the antigens recognized by these clones have been  
characterized.

The use of autologous CTLs for identifying tumor antigens requires that the target cells  
which express the antigens can be cultured *in vitro* and that stable lines of autologous CTL  
clones which recognize the antigen-expressing cells can be isolated and propagated. While this  
20 approach has worked well for melanoma antigens, other tumor types, such as epithelial cancers  
including breast and colon cancer, have proved refractory to the approach.

More recently another approach to the problem has been described by Sahin et al. (*Proc.  
Natl. Acad. Sci. USA* 92:11810-11813, 1995). According to this approach, autologous antisera  
are used to identify immunogenic protein antigens expressed in cancer cells by screening  
25 expression libraries constructed from tumor cell cDNA. Antigen-encoding clones so identified  
have been found to have elicited an high-titer humoral immune response in the patients from  
which the antisera were obtained. Such a high-titer IgG response implies helper T cell  
recognition of the detected antigen. These tumor antigens can then be screened for the presence  
of MHC/HLA class I and class II motifs and reactivity with CTLs

30

The invention is elaborated upon in the disclosure which follows.

### Summary of the Invention

Autologous antibody screening has now been applied to cancer using antisera from cancer patients. Numerous cancer associated antigens have been identified. The invention provides, *inter alia*, isolated nucleic acid molecules, expression vectors containing those  
5 molecules and host cells transfected with those molecules. The invention also provides isolated proteins and peptides, antibodies to those proteins and peptides and CTLs which recognize the proteins and peptides. Fragments including functional fragments and variants of the foregoing also are provided. Kits containing the foregoing molecules additionally are provided. The foregoing can be used in the diagnosis, monitoring, research, or treatment of  
10 conditions characterized by the expression of one or more cancer associated antigens.

Prior to the present invention, only a handful of cancer associated genes had been identified in the past 20 years. The invention involves the surprising discovery of many genes, some previously known and many previously unknown, which are expressed in individuals who have cancer. These individuals all have serum antibodies against the proteins (or fragments  
15 thereof) encoded by these genes. Thus, abnormally expressed genes are recognized by the host's immune system and therefore can form a basis for diagnosis, monitoring and therapy.

The invention involves the use of a single material, a plurality of different materials and even large panels and combinations of materials. For example, a single gene, a single protein encoded by a gene, a single functional fragment thereof, a single antibody thereto, etc. can be  
20 used in methods and products of the invention. Likewise, pairs, groups and even panels of these materials can be used for diagnosis, monitoring and therapy. The pairs, groups or panels can involve 2, 3, 4, 5... to as many as 25, 50, 100 or more genes, gene products, fragments thereof or agents that recognize such materials. A plurality of such materials are not only useful in monitoring, typing, characterizing and diagnosing cells abnormally expressing such genes, but a  
25 plurality of such materials can be used therapeutically. An example of the use of a plurality of such materials for the prevention, delay of onset, amelioration, etc. of cancer cells, which express or will express such genes prophylactically or acutely. Any and all combinations of the genes, gene products, and materials which recognize the genes and gene products can be tested and identified for use according to the invention. It would be far too lengthy to recite all such  
30 combinations; those skilled in the art, particularly in view of the teaching contained herein, will readily be able to determine which combinations are most appropriate for which circumstances.

As will be clear from the following discussion, the invention has *in vivo* and *in vitro* uses,

including for therapeutic, diagnostic, monitoring and research purposes. One aspect of the invention is the ability to fingerprint a cell expressing a number of the genes identified according to the invention. Such fingerprints will be characteristic, for example, of the stage of the cancer, the type of the cancer, or even the effect in animal models of a therapy on a cancer.

5 Cells also can be screened to determine whether such cells abnormally express the genes identified according to the invention.

The invention, in one aspect, is a method of diagnosing a disorder characterized by expression of a cancer associated antigen precursor coded for by a nucleic acid molecule. The method involves the steps of contacting a biological sample isolated from a subject with an  
10 agent that specifically binds to the nucleic acid molecule, an expression product thereof, or a fragment of an expression product thereof complexed with an MHC, preferably an HLA, molecule, wherein the nucleic acid molecule is a NA Group 1 nucleic acid molecule, and determining the interaction between the agent and the nucleic acid molecule, the expression product or fragment of the expression product as a determination of the disorder.

15 In one embodiment the agent is selected from the group consisting of (a) a nucleic acid molecule comprising NA Group 1 nucleic acid molecules or a fragment thereof, (b) a nucleic acid molecule comprising NA Group 3 nucleic acid molecules or a fragment thereof, (c) a nucleic acid molecule comprising NA Group 17 nucleic acid molecules or a fragment thereof, (d) an antibody that binds to an expression product, or a fragment thereof, of NA group 1  
20 nucleic acids, (e) an antibody that binds to an expression product, or a fragment thereof, of NA group 3 nucleic acids, (f) an antibody that binds to an expression product, or a fragment thereof, of NA group 17 nucleic acids, (g) and agent that binds to a complex of an MHC, preferably HLA, molecule and a fragment of an expression product of a NA Group 1 nucleic acid, (h) an agent that binds to a complex of an MHC, preferably HLA, molecule and a  
25 fragment of an expression product of a NA group 3 nucleic acid, and (I) an agent that binds to a complex of an MHC, preferably HLA, molecule and a fragment of an expression product of a NA Group 17 nucleic acid.

The disorder may be characterized by expression of a plurality of cancer associated antigen precursors and wherein the agent is a plurality of agents, each of which is specific for  
30 a different human cancer associated antigen precursor, and wherein said plurality of agents is at least 2, at least 3, at least 4, at least 5, at least 6, at least 7, at least 8, at least 9 or at least 10 such agents.

In each of the above embodiments the agent may be specific for a human cancer associated antigen precursor that is a breast, a gastric, a lung, a prostate, a renal or a colon cancer associated antigen precursor.

In another aspect the invention is a method for determining regression, progression or onset of a condition characterized by expression of abnormal levels of a protein encoded by a nucleic acid molecule that is a NA Group 1 molecule. The method involves the steps of monitoring a sample, from a subject who has or is suspected of having the condition, for a parameter selected from the group consisting of (i) the protein, (ii) a peptide derived from the protein, (iii) an antibody which selectively binds the protein or peptide, and (iv) cytolytic T cells specific for a complex of the peptide derived from the protein and an MHC molecule, as a determination of regression, progression or onset of said condition. In one embodiment the sample is a body fluid, a body effusion or a tissue.

In another embodiment the step of monitoring comprises contacting the sample with a detectable agent selected from the group consisting of (a) an antibody which selectively binds the protein of (i), or the peptide of (ii), (b) a protein or peptide which binds the antibody of (iii), and (c) a cell which presents the complex of the peptide and MHC molecule of (iv). In a preferred embodiment the antibody, the protein, the peptide or the cell is labeled with a radioactive label or an enzyme. The sample in a preferred embodiment is assayed for the peptide.

According to another embodiment the nucleic acid molecule is one of the following: a NA Group 3 molecule, a NA Group 11 molecule, a NA Group 12 molecule, a NA Group 13 molecule, a NA Group 14 molecule, a NA Group 15 molecule, or a NA Group 16 molecule. In yet another embodiment the protein is a plurality of proteins, the parameter is a plurality of parameters, each of the plurality of parameters being specific for a different of the plurality of proteins.

The invention in another aspect is a pharmaceutical preparation for a human subject. The pharmaceutical preparation includes an agent which when administered to the subject enriches selectively the presence of complexes of an HLA molecule and a human cancer associated antigen, and a pharmaceutically acceptable carrier, wherein the human cancer associated antigen is a fragment of a human cancer associated antigen precursor encoded by a nucleic acid molecule which comprises a NA Group 1 molecule. In one embodiment the nucleic acid molecule is a NA Group 3 nucleic acid molecule.

The agent in one embodiment comprises a plurality of agents, each of which enriches selectively in the subject complexes of an HLA molecule and a different human cancer associated antigen. Preferably the plurality is at least two, at least three, at least four or at least 5 different such agents.

5 In another embodiment the agent is selected from the group consisting of (1) an isolated polypeptide comprising the human cancer associated antigen, or a functional variant thereof, (2) an isolated nucleic acid operably linked to a promoter for expressing the isolated polypeptide, or functional variant thereof, (3) a host cell expressing the isolated polypeptide, or functional variant thereof, and (4) isolated complexes of the polypeptide, or functional  
10 variant thereof, and an HLA molecule.

The agent may be a cell expressing an isolated polypeptide. In one embodiment the agent is a cell expressing an isolated polypeptide comprising the human cancer associated antigen or a functional variant thereof, and wherein the cell is nonproliferative. In another embodiment the agent is a cell expressing an isolated polypeptide comprising the human cancer  
15 associated antigen or a functional variant thereof, and wherein the cell expresses an HLA molecule that binds the polypeptide. The cell can express one or both of the polypeptide and HLA molecule recombinantly. In another preferred embodiment the cell is nonproliferative. In yet another embodiment the agent is at least two, at least three, at least four or at least five different polypeptides, each representing a different human cancer associated antigen or  
20 functional variant thereof.

The agent in one embodiment is a PP Group 2 polypeptide. In other embodiments the agent is a PP Group 3 polypeptide or a PP Group 4 polypeptide.

In an embodiment each of the pharmaceutical preparations described herein also includes an adjuvant.

25 According to another aspect the invention, a composition is provided of an isolated agent that binds selectively a PP Group 1 polypeptide. In separate embodiments the agent binds selectively to a polypeptide selected from the following: a PP Group 3 polypeptide, a PP Group 11 polypeptide, a PP Group 12 polypeptide, a PP Group 13 polypeptide, a PP Group 14 polypeptide, a PP Group 15 polypeptide, and a PP Group 16 polypeptide. In other  
30 embodiments, the agent is a plurality of different agents that bind selectively at least two, at least three, at least four, or at least five different such polypeptides. In each of the above described embodiments the agent may be an antibody.

In another aspect the invention is a composition of matter composed of a conjugate of the agent of the above-described compositions of the invention and a therapeutic or diagnostic agent. Preferably the conjugate is of the agent and a therapeutic or diagnostic that is an antineoplastic.

5       The invention in another aspect is a pharmaceutical composition of an isolated nucleic acid molecule selected from the group consisting of: (1) NA Group 1 molecules, and (2) NA Group 2 molecules, and a pharmaceutically acceptable carrier. In one embodiment the isolated nucleic acid molecule comprises a NA Group 3 or NA Group 4 molecule. In another  
10       embodiment the isolated nucleic acid molecule comprises at least two isolated nucleic acid molecules coding for two different polypeptides, each polypeptide comprising a different cancer associated antigen.

      Preferably the pharmaceutical composition also includes an expression vector with a promoter operably linked to the isolated nucleic acid molecule. In another embodiment the pharmaceutical composition also includes a host cell recombinantly expressing the isolated  
15       nucleic acid molecule.

      According to another aspect of the invention a pharmaceutical composition is provided. The pharmaceutical composition includes an isolated polypeptide comprising a PP Group 1 or a PP Group 2 polypeptide, and a pharmaceutically acceptable carrier. In one embodiment the isolated polypeptide comprises a PP Group 3 or a PP Group 4 polypeptide.

20       In another embodiment the isolated polypeptide comprises at least two different polypeptides, each comprising a different cancer associated antigen. In separate embodiments the isolated polypeptides are selected from the following: PP Group 11 polypeptides or HLA binding fragments thereof, PP Group 12 polypeptides or HLA binding fragments thereof, PP Group 13 polypeptides or HLA binding fragments thereof, PP Group 14 polypeptides or HLA  
25       binding fragments thereof, PP Group 15 polypeptides or HLA binding fragments thereof, or PP Group 16 polypeptides or HLA binding fragments thereof.

      In an embodiment each of the pharmaceutical compositions described herein also includes an adjuvant.

      Another aspect the invention is an isolated nucleic acid molecule comprising a NA  
30       Group 3 molecule. Another aspect the invention is an isolated nucleic acid molecule comprising a NA Group 4 molecule. In separate embodiments the isolated nucleic acid molecules are selected from the following: a Group 11 molecule or a functional fragment



thereof, a Group 12 molecule or a functional fragment thereof, a Group 13 molecule or a functional fragment thereof, a Group 14 molecule or a functional fragment thereof, a Group 15 molecule or a functional fragment thereof, or a Group 16 molecule or a functional fragment thereof.

5       The invention in another aspect is an isolated nucleic acid molecule selected from the group consisting of (a) a fragment of a nucleic acid selected from the group of nucleic acid molecules consisting of SEQ ID numbered below and comprising all nucleic acid sequences among SEQ ID NOs 1-816, of sufficient length to represent a sequence unique within the human genome, and identifying a nucleic acid encoding a human cancer associated antigen precursor, (b) complements of (a), provided that the fragment includes a sequence of  
10 contiguous nucleotides which is not identical to any sequence selected from the sequence group consisting of (1) sequences having the GenBank accession numbers of the sequence Group 1, (2) complements of (1), and (3) fragments of (1) and (2).

In one embodiment the sequence of contiguous nucleotides is selected from the group  
15 consisting of: (1) at least two contiguous nucleotides nonidentical to the sequence Group 1, (2) at least three contiguous nucleotides nonidentical to the sequence Group 1, (3) at least four contiguous nucleotides nonidentical to the sequence Group 1, (4) at least five contiguous nucleotides nonidentical to the sequence Group 1, (5) at least six contiguous nucleotides nonidentical to the sequence Group 1, or (6) at least seven contiguous nucleotides nonidentical  
20 to the sequence Group 1.

In another embodiment the fragment has a size selected from the group consisting of at least: 8 nucleotides, 10 nucleotides, 12 nucleotides, 14 nucleotides, 16 nucleotides, 18 nucleotides, 20, nucleotides, 22 nucleotides, 24 nucleotides, 26 nucleotides, 28 nucleotides, 30 nucleotides, 50 nucleotides, 75 nucleotides, 100 nucleotides, 200 nucleotides, 1000 nucleotides  
25 and every integer length therebetween.

In yet another embodiment the molecule encodes a polypeptide which, or a fragment of which, binds a human HLA receptor or a human antibody.

Another aspect of the invention is an expression vector comprising an isolated nucleic acid molecule of the invention described above operably linked to a promoter.

30       According to one aspect the invention is an expression vector comprising a nucleic acid operably linked to a promoter, wherein the nucleic acid is a NA Group 2 molecule. In another aspect the invention is an expression vector comprising a NA Group 1 or Group 2 molecule

and a nucleic acid encoding an MHC, preferably HLA, molecule.

In yet another aspect the invention is a host cell transformed or transfected with an expression vector of the invention described above.

In another aspect the invention is a host cell transformed or transfected with an  
5 expression vector comprising an isolated nucleic acid molecule of the invention described  
above operably linked to a promoter, or an expression vector comprising a nucleic acid  
operably linked to a promoter, wherein the nucleic acid is a NA Group 1 or 2 molecule and  
further comprising a nucleic acid encoding HLA.

According to another aspect of the invention an isolated polypeptide encoded by the  
10 isolated nucleic acid molecules the invention, described above, is provided. These include PP  
Group 1-17 polypeptides. The invention also includes a fragment of the polypeptide which is  
immunogenic. In one embodiment the fragment, or a portion of the fragment, binds HLA or a  
human antibody.

The invention includes in another aspect an isolated fragment of a human cancer  
15 associated antigen precursor which, or portion of which, binds HLA or a human antibody,  
wherein the precursor is encoded by a nucleic acid molecule that is a NA Group 1 molecule.  
In one embodiment the fragment is part of a complex with HLA. In another embodiment the  
fragment is between 8 and 12 amino acids in length. In another embodiment the invention  
includes an isolated polypeptide comprising a fragment of the polypeptide of sufficient length  
20 to represent a sequence unique within the human genome and identifying a polypeptide that is  
a human cancer associated antigen precursor.

According to another aspect of the invention a kit for detecting the presence of the  
expression of a cancer associated antigen precursor is provided. The kit includes a pair of  
isolated nucleic acid molecules each of which consists essentially of a molecule selected from  
25 the group consisting of (a) a 12-32 nucleotide contiguous segment of the nucleotide sequence  
of any of the NA Group 1 molecules and (b) complements of ("a"), wherein the contiguous  
segments are nonoverlapping. In one embodiment the pair of isolated nucleic acid molecules  
is constructed and arranged to selectively amplify an isolated nucleic acid molecule that is a  
NA Group 3 molecule. Preferably, the pair amplifies a human NA Group 3 molecule.

30 According to another aspect of the invention a method for treating a subject with a  
disorder characterized by expression of a human cancer associated antigen precursor is  
provided. The method includes the step of administering to the subject an amount of an agent.

which enriches selectively in the subject the presence of complexes of an HLA molecule and a human cancer associated antigen, effective to ameliorate the disorder, wherein the human cancer associated antigen is a fragment of a human cancer associated antigen precursor encoded by a nucleic acid molecule selected from the group consisting of (a) a nucleic acid molecule comprising NA group 1 nucleic acid molecules, (b) a nucleic acid molecule comprising NA group 3 nucleic acid molecules, (c) a nucleic acid molecule comprising NA group 17 nucleic acid molecules.

In one embodiment the disorder is characterized by expression of a plurality of human cancer associated antigen precursors and wherein the agent is a plurality of agents, each of which enriches selectively in the subject the presence of complexes of an HLA molecule and a different human cancer associated antigen. Preferably the plurality is at least 2, at least 3, at least 4, or at least 5 such agents.

In another embodiment the agent is an isolated polypeptide selected from the group consisting of PP Group 1, PP Group 2, PP Group 3, PP Group 4, PP Group 5, PP Group 6, PP Group 7, PP Group 8, PP Group 9, PP Group 10, PP Group 11, PP Group 12, PP Group 13, PP Group 14, PP Group 15, PP Group 16 and PP Group 17 polypeptides.

In yet another embodiment the disorder is cancer.

According to another aspect the invention is a method for treating a subject having a condition characterized by expression of a cancer associated antigen precursor in cells of the subject. The method includes the steps of (i) removing an immunoreactive cell containing sample from the subject, (ii) contacting the immunoreactive cell containing sample to the host cell under conditions favoring production of cytolytic T cells against a human cancer associated antigen which is a fragment of the precursor, (iii) introducing the cytolytic T cells to the subject in an amount effective to lyse cells which express the human cancer associated antigen, wherein the host cell is transformed or transfected with an expression vector comprising an isolated nucleic acid molecule operably linked to a promoter, the isolated nucleic acid molecule being selected from the group of nucleic acid molecules consisting of NA Group 1, NA Group 2, NA Group 3, NA Group 4, NA Group 5, NA Group 6, NA Group 7, NA Group 8, NA Group 9, NA Group 10, NA Group 11, NA Group 12, NA Group 13, NA Group 14, NA Group 15, NA Group 16, and NA Group 17.

In one embodiment the host cell recombinantly expresses an HLA molecule which binds the human cancer associated antigen. In another embodiment the host cell endogenously

expresses an HLA molecule which binds the human cancer associated antigen.

The invention includes in another aspect a method for treating a subject having a condition characterized by expression of a cancer associated antigen precursor in cells of the subject. The method includes the steps of (I) identifying a nucleic acid molecule expressed by the cells associated with said condition, wherein said nucleic acid molecule is a NA Group 1 molecule (ii) transfecting a host cell with a nucleic acid selected from the group consisting of (a) the nucleic acid molecule identified, (b) a fragment of the nucleic acid identified which includes a segment coding for a cancer associated antigen, (c) deletions, substitutions or additions to (a) or (b), and (d) degenerates of (a), (b), or (c); (iii) culturing said transfected host cells to express the transfected nucleic acid molecule, and; (iv) introducing an amount of said host cells or an extract thereof to the subject effective to increase an immune response against the cells of the subject associated with the condition. Preferably, the antigen is a human antigen and the subject is a human.

In one embodiment the method also includes the step of (a) identifying an MHC molecule which presents a portion of an expression product of the nucleic acid molecule, wherein the host cell expresses the same MHC molecule as identified in (a) and wherein the host cell presents an MHC binding portion of the expression product of the nucleic acid molecule.

In another embodiment the method also includes the step of treating the host cells to render them non-proliferative.

In yet another embodiment the immune response comprises a B-cell response or a T cell response. Preferably the response is a T-cell response which comprises generation of cytolytic T-cells specific for the host cells presenting the portion of the expression product of the nucleic acid molecule or cells of the subject expressing the human cancer associated antigen.

In another embodiment the nucleic acid molecule is a NA Group 3 molecule.

Another aspect of the invention is a method for treating or diagnosing or monitoring a subject having a condition characterized by expression of an abnormal amount of a protein encoded by a nucleic acid molecule that is a NA Group 1 molecule. The method includes the step of administering to the subject an antibody which specifically binds to the protein or a peptide derived therefrom, the antibody being coupled to a therapeutically useful agent, in an amount effective to treat the condition.

In one embodiment the antibody is a monoclonal antibody. Preferably the monoclonal antibody is a chimeric antibody or a humanized antibody.

In another aspect the invention is a method for treating a condition characterized by expression in a subject of abnormal amounts of a protein encoded by a nucleic acid molecule that is a NA Group 1 nucleic acid molecule. The method involves the step of administering to a subject at least one of the pharmaceutical compositions of the invention described above in an amount effective to prevent, delay the onset of, or inhibit the condition in the subject. In one embodiment the condition is cancer. In another embodiment the method includes the step of first identifying that the subject expresses in a tissue abnormal amounts of the protein.

10 The invention in another aspect is a method for treating a subject having a condition characterized by expression of abnormal amounts of a protein encoded by a nucleic acid molecule that is a NA Group 1 nucleic acid molecule. The method includes the steps of (i) identifying cells from the subject which express abnormal amounts of the protein; (ii) isolating a sample of the cells; (iii) cultivating the cells, and (iv) introducing the cells to the subject in an amount effective to provoke an immune response against the cells.

15

In one embodiment the cells express a protein selected from the group consisting of a PP Group 11 protein, a PP Group 12 protein, a PP Group 13 protein, PP Group 14 protein, a PP Group 15 protein and a PP Group 16 protein. In another embodiment the method includes the step of rendering the cells non-proliferative, prior to introducing them to the subject.

20 In another aspect the invention is a method for treating a pathological cell condition characterized by abnormal expression of a protein encoded by a nucleic acid molecule that is a NA Group 1 nucleic acid molecule. The method includes the step of administering to a subject in need thereof an effective amount of an agent which inhibits the expression or activity of the protein.

25 In one embodiment the agent is an inhibiting antibody which selectively binds to the protein and wherein the antibody is a monoclonal antibody, a chimeric antibody or a humanized antibody. In another embodiment the agent is an antisense nucleic acid molecule which selectively binds to the nucleic acid molecule which encodes the protein. In yet another important embodiment the nucleic acid molecule is a NA Group 3 nucleic acid molecule.

30 The invention includes in another aspect a composition of matter useful in stimulating an immune response to a plurality of a protein encoded by nucleic acid molecules that are NA Group 1 molecules. The composition is a plurality of peptides derived from the amino acid

sequences of the proteins, wherein the peptides bind to one or more MHC molecules presented on the surface of the cells which express an abnormal amount of the protein.

In one embodiment at least a portion of the plurality of peptides bind to MHC molecules and elicit a cytolytic response thereto. In another embodiment the composition of matter includes an adjuvant. In another embodiment the adjuvant is a saponin, GM-CSF, or an interleukin.

According to another aspect the invention is an isolated antibody which selectively binds to a complex of: (I) a peptide derived from a protein encoded by a nucleic acid molecule that is a NA Group 1 molecule and (ii) and an MHC molecule to which binds the peptide to form the complex, wherein the isolated antibody does not bind to (I) or (ii) alone.

In one embodiment the antibody is a monoclonal antibody, a chimeric antibody or a humanized antibody.

The invention also involves the use of the genes, gene products, fragments thereof, agents which bind thereto, and so on in the preparation of medicaments. A particular medicament is for treating cancer and a more particular medicament is for treating breast cancer, lung cancer, renal cancer, colon cancer, prostate cancer or gastric cancer.

### **Detailed Description of the Invention**

In the above summary and in the ensuing description, lists of sequences are provided.

The lists are meant to embrace each single sequence separately, two or more sequences together where they form a part of the same gene, any combination of two or more sequences which relate to different genes, including and up to the total number on the list, as if each and every combination were separately and specifically enumerated. Likewise, when mentioning fragment size, it is intended that a range embrace the smallest fragment mentioned to the full-length of the sequence (-1 so that it is a fragment), each and every fragment length intended as if specifically enumerated. Thus, if a fragment could be between 10 and 15 in length, it is explicitly meant to mean 10, 11, 12, 13, 14, or 15 in length.

The summary and the claims mention antigen precursors and antigens. As used in the summary and in the claims, a precursor is substantially the full-length protein encoded by the coding region of the isolated DNA and the antigen is a peptide which complexes with MHC, preferably HLA, and which participates in the immune response as part of that complex. Such antigens are typically 9 amino acids long, although this may vary slightly.

As used herein, a subject is a human, non-human primate, cow, horse, pig, sheep, goat, dog, cat or rodent. In all embodiments human cancer antigens and human subjects are preferred.

The present invention in one aspect involves the cloning of cDNAs encoding human cancer associated antigen precursors using autologous antisera of subjects having cancer. The sequences of the clones representing genes identified according to the methods described herein are presented in the attached Sequence Listing, and the predicted amino acid sequences of some clones also are presented. Of the foregoing, it can be seen that some of the clones are considered completely novel as no nucleotide or amino acid homologies to coding regions were found in the databases searched. Other clones are novel but have some homology to sequences deposited in databases (mainly EST sequences). Nevertheless, the entire gene sequence was not previously known. In some cases no function was suspected and in other cases, even if a function was suspected, it was not known that the gene was associated with cancer. In all cases, it was not known or suspected that the gene encoded a cancer antigen which reacted with antibody from autologous sera. Analysis of the clone sequences by comparison to nucleic acid and protein databases determined that still other of the clones surprisingly are closely related to other previously-cloned genes. The sequences of these related genes is also presented in the Sequence Listing. The nature of the foregoing genes as encoding antigens recognized by the immune systems of cancer patients is, of course, unexpected.

The invention thus involves in one aspect cancer associated antigen polypeptides, genes encoding those polypeptides, functional modifications and variants of the foregoing, useful fragments of the foregoing, as well as diagnostics and therapeutics relating thereto.

Homologs and alleles of the cancer associated antigen nucleic acids of the invention can be identified by conventional techniques. Thus, an aspect of the invention is those nucleic acid sequences which code for cancer associated antigen precursors. Because this application contains so many sequences, the following chart is provided to identify the various groups of sequences discussed in the claims and in the summary:

#### "Nucleic Acid Sequences"

NA Group 1. (a) nucleic acid molecules which hybridize under stringent conditions to a molecule consisting of a nucleic acid sequence selected from the group consisting of nucleic acid sequences among SEQ ID NOs 1-816 and which code for a cancer associated antigen precursor.

(b) deletions, additions and substitutions which code for a respective cancer associated antigen precursor,

(c) nucleic acid molecules that differ from the nucleic acid molecules of (a) or (b) in codon sequence due to the degeneracy of the genetic code, and

5 (d) complements of (a), (b) or (c).

NA Group 2. Fragments of NA Group 1, which codes for a polypeptide which, or a portion of which, binds an MHC molecule to form a complex recognized by a an autologous antibody or lymphocyte.

10

NA Group 3. The subset of NA Group 1 where the nucleotide sequence is selected from the group consisting of:

(a) previously unknown human nucleic acids coding for a human cancer associated antigen precursor,

15 (b) deletions, additions and substitutions which code for a respective human cancer associated antigen precursor,

(c) nucleic acid molecules that differ from the nucleic acid molecules of (a) or (b) in codon sequence due to the degeneracy of the genetic code, and

(d) complements of (a), (b) or (c).

20 NA Group 4. Fragments of NA Group 3, which code for a polypeptide which, or a portion of which, binds to an MHC molecule to form a complex recognized by an autologous antibody or lymphocyte.

NA Group 5. A subset of NA Group 1, wherein the nucleic acid molecule codes for a human  
25 breast cancer associated antigen precursor.

NA Group 6. A subset of NA Group 1, wherein the nucleic acid molecule codes for a human colon cancer associated antigen precursor.

30 NA Group 7. A subset of NA Group 1, wherein the nucleic acid molecule codes for a human gastric cancer associated antigen precursor.



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NA Group 8. A subset of NA Group 1, wherein the nucleic acid molecule codes for a human lung cancer associated antigen precursor.

NA Group 9. A subset of NA Group 1, wherein the nucleic acid molecule codes for a human  
5 renal cancer associated antigen precursor.

NA Group 10. A subset of NA Group 1, wherein the nucleic acid molecule codes for a human prostate cancer associated antigen precursor.

10 NA Group 11. A subset of NA Group 3, wherein the nucleic acid molecule codes for a human breast cancer associated antigen precursor.

NA Group 12. A subset of NA Group 3, wherein the nucleic acid molecule codes for a human colon cancer associated antigen precursor.

15

NA Group 13. A subset of NA Group 3, wherein the nucleic acid molecule codes for a human gastric cancer associated antigen precursor.

NA Group 14. A subset of NA Group 3, wherein the nucleic acid molecule codes for a human  
20 lung cancer associated antigen precursor.

NA Group 15. A subset of NA Group 3, wherein the nucleic acid molecule codes for a human renal cancer associated antigen precursor.

25 NA Group 16. A subset of NA Group 3, wherein the nucleic acid molecule codes for a human prostate cancer associated antigen precursor.

NA Group 17. A subset of NA Group 1, comprising human cancer associated antigens that react with allogenic cancer antisera.

30

#### Polypeptide Sequences

PP Group 1. Polypeptides encoded by NA Group 1.

- PP Group 2. Polypeptides encoded by NA Group 2  
PP Group 3. Polypeptides encoded by NA Group 3.  
PP Group 4. Polypeptides encoded by NA Group 4.  
PP Group 5. Polypeptides encoded by NA Group 5.  
5 PP Group 6. Polypeptides encoded by NA Group 6.  
PP Group 7. Polypeptides encoded by NA Group 7.  
PP Group 8. Polypeptides encoded by NA Group 8.  
PP Group 9. Polypeptides encoded by NA Group 9.  
PP Group 10. Polypeptides encoded by NA Group 10.  
10 PP Group 11. Polypeptides encoded by NA Group 11.  
PP Group 12. Polypeptides encoded by NA Group 12.  
PP Group 13. Polypeptides encoded by NA Group 13.  
PP Group 14. Polypeptides encoded by NA Group 14.  
PP Group 15. Polypeptides encoded by NA Group 15.  
15 PP Group 16. Polypeptides encoded by NA Group 16.  
PP Group 17. Polypeptides encoded by NA Group 17.

The term "stringent conditions" as used herein refers to parameters with which the art is familiar. Nucleic acid hybridization parameters may be found in references which compile such  
20 methods, e.g. *Molecular Cloning: A Laboratory Manual*, J. Sambrook, et al., eds., Second Edition, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, New York, 1989, or *Current Protocols in Molecular Biology*, F.M. Ausubel, et al., eds., John Wiley & Sons, Inc., New York. More specifically, stringent conditions, as used herein, refers, for example, to hybridization at  
65°C in hybridization buffer (3.5 x SSC, 0.02% Ficoll, 0.02% polyvinyl pyrrolidone, 0.02%  
25 Bovine Serum Albumin, 2.5mM NaH<sub>2</sub>PO<sub>4</sub>(pH7), 0.5% SDS, 2mM EDTA). SSC is 0.15M sodium chloride/0.15M sodium citrate, pH7; SDS is sodium dodecyl sulphate; and EDTA is ethylenediaminetetracetic acid. After hybridization, the membrane upon which the DNA is transferred is washed, for example, in 2 x SSC at room temperature and then at 0.1 - 0.5 x  
SSC/0.1 x SDS at temperatures up to 68°C.

30 There are other conditions, reagents, and so forth which can be used, which result in a similar degree of stringency. The skilled artisan will be familiar with such conditions, and thus they are not given here. It will be understood, however, that the skilled artisan will be able to

manipulate the conditions in a manner to permit the clear identification of homologs and alleles of cancer associated antigen nucleic acids of the invention (e.g., by using lower stringency conditions). The skilled artisan also is familiar with the methodology for screening cells and libraries for expression of such molecules which then are routinely isolated, followed by  
5 isolation of the pertinent nucleic acid molecule and sequencing.

In general homologs and alleles typically will share at least 40% nucleotide identity and/or at least 50% amino acid identity to the sequences of breast cancer associated antigen nucleic acid and polypeptides, respectively, in some instances will share at least 50% nucleotide identity and/or at least 65% amino acid identity and in still other instances will share at least 60%  
10 nucleotide identity and/or at least 75% amino acid identity. The homology can be calculated using various, publicly available software tools developed by NCBI (Bethesda, Maryland) that can be obtained through the internet (<ftp://ncbi.nlm.nih.gov/pub/>). Exemplary tools include the BLAST system available at <http://www.ncbi.nlm.nih.gov>. Pairwise and ClustalW alignments (BLOSUM30 matrix setting) as well as Kyte-Doolittle hydropathic analysis can be obtained  
15 using the MacVector sequence analysis software (Oxford Molecular Group). Watson-Crick complements of the foregoing nucleic acids also are embraced by the invention.

In screening for cancer associated antigen genes, a Southern blot may be performed using the foregoing conditions, together with a radioactive probe. After washing the membrane to which the DNA is finally transferred, the membrane can be placed against X-ray film to detect  
20 the radioactive signal. In screening for the expression of cancer associated antigen nucleic acids, Northern blot hybridizations using the foregoing conditions (see also the Examples) can be performed on samples taken from breast cancer patients or subjects suspected of having a condition characterized by expression of breast cancer associated antigen genes. Amplification protocols such as polymerase chain reaction using primers which hybridize to the sequences  
25 presented also can be used for detection of the cancer associated antigen genes or expression thereof.

The breast cancer associated genes correspond to SEQ ID NOs. 1-40 and 66. The preferred breast cancer associated antigens for the methods of diagnosis disclosed herein are those set forth in SEQ ID NOs: [31, 33 and 34], which were found to react with allogeneic breast  
30 cancer antisera. Encoded polypeptides (e.g., proteins), peptides and antisera thereto are also preferred for diagnosis.

The colon cancer associated genes correspond to SEQ ID Nos. 544-586, even numbers

only. The preferred colon cancer associated antigens for the methods of diagnosis disclosed herein are those, which were found to react with allogeneic colon cancer antisera. Encoded polypeptides (e.g., proteins), peptides and antisera thereto are also preferred for diagnosis.

The gastric cancer associated genes correspond to SEQ ID NOs 176-436 and 588-674.

5 The preferred gastric cancer associated antigens for the methods of diagnosis disclosed herein are those, which were found to react with allogeneic gastric cancer antisera. Encoded polypeptides (e.g., proteins), peptides and antisera thereto are also preferred for diagnosis.

The renal cancer associated genes correspond to SEQ ID Nos. 89-169, odd numbers only, and 170, 172, and 174. The preferred renal cancer associated antigens for the methods of  
10 diagnosis disclosed herein are those, which were found to react with allogeneic renal cancer antisera. Encoded polypeptides (e.g., proteins), peptides and antisera thereto are also preferred for diagnosis.

The lung cancer associated genes correspond to SEQ ID Nos. 689, 691, 692, 694, 696-707, 709, 711, and 712. The preferred lung cancer associated antigens for the methods of  
15 diagnosis disclosed herein are those, which were found to react with allogeneic lung cancer antisera. Encoded polypeptides (e.g., proteins), peptides and antisera thereto are also preferred for diagnosis.

The prostate cancer associated genes correspond to SEQ ID NOs 437-543. The preferred prostate cancer associated antigens for the methods of diagnosis disclosed herein are those,  
20 which were found to react with allogeneic prostate cancer antisera. Encoded polypeptides (e.g., proteins), peptides and antisera thereto are also preferred for diagnosis.

The invention also includes degenerate nucleic acids which include alternative codons to those present in the native materials. For example, serine residues are encoded by the codons TCA, AGT, TCC, TCG, TCT and AGC. Each of the six codons is equivalent for the purposes of  
25 encoding a serine residue. Thus, it will be apparent to one of ordinary skill in the art that any of the serine-encoding nucleotide triplets may be employed to direct the protein synthesis apparatus, *in vitro* or *in vivo*, to incorporate a serine residue into an elongating breast cancer associated antigen polypeptide. Similarly, nucleotide sequence triplets which encode other amino acid residues include, but are not limited to: CCA, CCC, CCG and CCT (proline codons); CGA,  
30 CGC, CGG, CGT, AGA and AGG (arginine codons); ACA, ACC, ACG and ACT (threonine codons); AAC and AAT (asparagine codons); and ATA, ATC and ATT (isoleucine codons). Other amino acid residues may be encoded similarly by multiple nucleotide sequences. Thus,

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the invention embraces degenerate nucleic acids that differ from the biologically isolated nucleic acids in codon sequence due to the degeneracy of the genetic code.

The invention also provides isolated unique fragments of cancer associated antigen nucleic acid sequences or complements thereof. A unique fragment is one that is a 'signature' for the larger nucleic acid. It, for example, is long enough to assure that its precise sequence is not found in molecules within the human genome outside of the cancer associated antigen nucleic acids defined above (and human alleles). Those of ordinary skill in the art may apply no more than routine procedures to determine if a fragment is unique within the human genome. Unique fragments, however, exclude fragments completely composed of the nucleotide sequences of any of GenBank accession numbers listed in Table 1 or other previously published sequences as of the filing date of the priority documents for sequences listed in a respective priority document or the filing date of this application for sequences listed for the first time in this application which overlap the sequences of the invention.

A fragment which is completely composed of the sequence described in the foregoing GenBank deposits is one which does not include any of the nucleotides unique to the sequences of the invention. Thus, a unique fragment must contain a nucleotide sequence other than the exact sequence of those in GenBank or fragments thereof. The difference may be an addition, deletion or substitution with respect to the GenBank sequence or it may be a sequence wholly separate from the GenBank sequence.

Unique fragments can be used as probes in Southern and Northern blot assays to identify such nucleic acids, or can be used in amplification assays such as those employing PCR. As known to those skilled in the art, large probes such as 200, 250, 300 or more nucleotides are preferred for certain uses such as Southern and Northern blots, while smaller fragments will be preferred for uses such as PCR. Unique fragments also can be used to produce fusion proteins for generating antibodies or determining binding of the polypeptide fragments, or for generating immunoassay components. Likewise, unique fragments can be employed to produce nonfused fragments of the cancer associated antigen polypeptides, useful, for example, in the preparation of antibodies, and in immunoassays. Unique fragments further can be used as antisense molecules to inhibit the expression of cancer associated antigen nucleic acids and polypeptides, particularly for therapeutic purposes as described in greater detail below.

As will be recognized by those skilled in the art, the size of the unique fragment will depend upon its conservancy in the genetic code. Thus, some regions of cancer associated antigen sequences and complements thereof will require longer segments to be unique while others will require only short segments, typically between 12 and 32 nucleotides (e.g. 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31 and 32 or more bases long, up to the entire length of the disclosed sequence. As mentioned above, this disclosure intends to embrace each and every fragment of each sequence, beginning at the first nucleotide, the second nucleotide and so on, up to 8 nucleotides short of the end, and ending anywhere from nucleotide number 8, 9, 10 and so on for each sequence, up to the very last nucleotide, (provided the sequence is unique as described above).

Virtually any segment of the polypeptide coding region of novel cancer associated antigen nucleic acids, or complements thereof, that is 18 or more nucleotides in length will be unique. Those skilled in the art are well versed in methods for selecting such sequences, typically on the basis of the ability of the unique fragment to selectively distinguish the sequence of interest from other sequences in the human genome of the fragment to those on known databases typically is all that is necessary, although *in vitro* confirmatory hybridization and sequencing analysis may be performed. Especially preferred include nucleic acids encoding a series of epitopes, known as "polytopes". The epitopes can be arranged in sequential or overlapping fashion (*see, e.g.,* Thomson et al., *Proc. Natl. Acad. Sci. USA* 92:5845-5849, 1995; Gilbert et al., *Nature Biotechnol.* 15:1280-1284, 1997), with or without the natural flanking sequences, and can be separated by unrelated linker sequences if desired. The polytope is processed to generated individual epitopes which are recognized by the immune system for generation of immune responses.

Thus, for example, peptides derived from a polypeptide having an amino acid sequence encoded by one of the nucleic acid disclosed herein, and which are presented by MHC molecules and recognized by CTL or T helper lymphocytes, can be combined with peptides from one or more other cancer associated antigens (e.g. by preparation of hybrid nucleic acids or polypeptides) to form "polytopes". The two or more peptides (or nucleic acids encoding the peptides) can be selected from those described herein, or they can include one or more peptides of previously known cancer associated antigens. Exemplary cancer associated peptide antigens that can be administered to induce or enhance an immune response are derived from tumor associated genes and encoded proteins including MAGE-1, MAGE-2, MAGE-3, MAGE-4, MAGE-5, MAGE-6, MAGE-7,

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MAGE-8, MAGE-9, MAGE-10, MAGE-11, GAGE-1, GAGE-2, GAGE-3, GAGE-4, GAGE-5, GAGE-6, BAGE-1, RAGE-1, LB33/MUM-1, PRAME, NAG, MAGE-Xp2, MAGE-Xp3, MAGE-Xp4, tyrosinase, brain glycogen phosphorylase, Melan-A, and MAGE-C1. See, for example, PCT application publication no. WO96/10577. Other examples will be known to one of ordinary skill in the art (for example, see Coulie, *Stem Cells* 13:393-403, 1995), and can be used in the invention in a like manner as those disclosed herein. One of ordinary skill in the art can prepare polypeptides comprising one or more peptides and one or more of the foregoing cancer associated peptides, or nucleic acids encoding such polypeptides, according to standard procedures of molecular biology.

Thus polytopes are groups of two or more potentially immunogenic or immune response stimulating peptides which can be joined together in various arrangements (e.g. concatenated, overlapping). The polytope (or nucleic acid encoding the polytope) can be administered in a standard immunization protocol, e.g. to animals, to test the effectiveness of the polytope in stimulating, enhancing and/or provoking an immune response.

The peptides can be joined together directly or via the use of flanking sequences to form polytopes, and the use of polytopes as vaccines is well known in the art (see, e.g., Thomson et al., *Proc. Acad. Natl. Acad. Sci USA* 92(13):5845-5849, 1995; Gilbert et al., *Nature Biotechnol.* 15(12):1280-1284, 1997; Thomson et al., *J. Immunol.* 157(2):822-826, 1996; Tam et al., *J. Exp. Med.* 171(1):299-306, 1990). for example, Tam showed that polytopes consisting of both MHC class I and class II binding epitopes successfully generated antibody and protective immunity in a mouse model. Tam also demonstrated that polytopes comprising "strings" of epitopes are processed to yield individual epitopes which are presented by MHC molecules and recognized by CTLs. Thus polytopes containing various numbers and combinations of epitopes can be prepared and tested for recognition by CTLs and for efficacy in increasing an immune response.

It is known that tumors express a set of tumor antigens, of which only certain subsets may be expressed in the tumor of any given patient (for examples of this, see the Examples below).

Polytopes can be prepared which correspond to the different combination of epitopes representing the subset of tumor rejection antigens expressed in a particular patient. Polytopes also can be prepared to reflect a broader spectrum of tumor rejection antigens known to be expressed by a tumor type. Polytopes can be introduced to a patient in need of such treatment as polypeptide structures, or via the use of nucleic acid delivery systems known in the art (see, e.g., Allsopp et al., *Eur. J.*

*Immunol.* 26(8):1951-1959, 1996). Adenovirus, pox virus, Ty-virus like particles, adeno-associated virus, plasmids, bacteria, etc. can be used in such delivery. One can test the polytope delivery systems in mouse models to determine efficacy of the delivery system. The systems also can be tested in human clinical trials.

5 In instances in which a human HLA class I molecule presents tumor rejection antigens derived from cancer associated nucleic acids, the expression vector may also include a nucleic acid sequence coding for the HLA molecule that presents any particular tumor rejection antigen derived from these nucleic acids and polypeptides. Alternatively, the nucleic acid sequence coding for such a HLA molecule can be contained within a separate expression vector. In a situation where the  
10 vector contains both coding sequences, the single vector can be used to transfect a cell which does not normally express either one. Where the coding sequences for a cancer associated antigen precursor and the HLA molecule which presents it are contained on separate expression vectors, the expression vectors can be cotransfected. The cancer associated antigen precursor coding sequence may be used alone, when, e.g. the host cell already expresses a HLA molecule which presents a  
15 cancer associated antigen derived from precursor molecules. Of course, there is no limit on the particular host cell which can be used. As the vectors which contain the two coding sequences may be used in any antigen-presenting cells if desired, and the gene for cancer associated antigen precursor can be used in host cells which do not express a HLA molecule which presents a cancer associated antigen. Further, cell-free transcription systems may be used in lieu of cells.

20 As mentioned above, the invention embraces antisense oligonucleotides that selectively bind to a nucleic acid molecule encoding a cancer associated antigen polypeptide, to reduce the expression of cancer associated antigens. This is desirable in virtually any medical condition wherein a reduction of expression of cancer associated antigens is desirable, e.g., in the treatment of cancer. This is also useful for *in vitro* or *in vivo* testing of the effects of a reduction of expression of  
25 one or more cancer associated antigens.

As used herein, the term "antisense oligonucleotide" or "antisense" describes an oligonucleotide that is an oligoribonucleotide, oligodeoxyribonucleotide, modified oligoribonucleotide, or modified oligodeoxyribonucleotide which hybridizes under physiological conditions to DNA comprising a particular gene or to an mRNA transcript of that gene and, thereby,  
30 inhibits the transcription of that gene and/or the translation of that mRNA. The antisense molecules



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are designed so as to interfere with transcription or translation of a target gene upon hybridization with the target gene or transcript. Those skilled in the art will recognize that the exact length of the antisense oligonucleotide and its degree of complementarity with its target will depend upon the specific target selected, including the sequence of the target and the particular bases which comprise that sequence. It is preferred that the antisense oligonucleotide be constructed and arranged so as to bind selectively with the target under physiological conditions, i.e., to hybridize substantially more to the target sequence than to any other sequence in the target cell under physiological conditions. Based upon the sequences of nucleic acids encoding breast cancer associated antigen, or upon allelic or homologous genomic and/or cDNA sequences, one of skill in the art can easily choose and synthesize any of a number of appropriate antisense molecules for use in accordance with the present invention. In order to be sufficiently selective and potent for inhibition, such antisense oligonucleotides should comprise at least 10 and, more preferably, at least 15 consecutive bases which are complementary to the target, although in certain cases modified oligonucleotides as short as 7 bases in length have been used successfully as antisense oligonucleotides (Wagner et al., *Nature Biotechnol.* 14:840-844, 1996). Most preferably, the antisense oligonucleotides comprise a complementary sequence of 20-30 bases. Although oligonucleotides may be chosen which are antisense to any region of the gene or mRNA transcripts, in preferred embodiments the antisense oligonucleotides correspond to N-terminal or 5' upstream sites such as translation initiation, transcription initiation or promoter sites. In addition, 3'-untranslated regions may be targeted. Targeting to mRNA splicing sites has also been used in the art but may be less preferred if alternative mRNA splicing occurs. In addition, the antisense is targeted, preferably, to sites in which mRNA secondary structure is not expected (see, e.g., Sainio et al., *Cell Mol. Neurobiol.* 14(5):439-457, 1994) and at which proteins are not expected to bind. Finally, although the listed sequences are cDNA sequences, one of ordinary skill in the art may easily derive the genomic DNA corresponding to the cDNA of a cancer associated antigen. Thus, the present invention also provides for antisense oligonucleotides which are complementary to the genomic DNA corresponding to nucleic acids encoding breast cancer associated antigens. Similarly, antisense to allelic or homologous cDNAs and genomic DNAs are enabled without undue experimentation.

In one set of embodiments, the antisense oligonucleotides of the invention may be composed of "natural" deoxyribonucleotides, ribonucleotides, or any combination thereof. That is, the 5' end

of one native nucleotide and the 3' end of another native nucleotide may be covalently linked, as in natural systems, via a phosphodiester internucleoside linkage. These oligonucleotides may be prepared by art recognized methods which may be carried out manually or by an automated synthesizer. They also may be produced recombinantly by vectors.

5 In preferred embodiments, however, the antisense oligonucleotides of the invention also may include "modified" oligonucleotides. That is, the oligonucleotides may be modified in a number of ways which do not prevent them from hybridizing to their target but which enhance their stability or targeting or which otherwise enhance their therapeutic effectiveness.

The term "modified oligonucleotide" as used herein describes an oligonucleotide in which  
10 (1) at least two of its nucleotides are covalently linked via a synthetic internucleoside linkage (i.e., a linkage other than a phosphodiester linkage between the 5' end of one nucleotide and the 3' end of another nucleotide) and/or (2) a chemical group not normally associated with nucleic acids has been covalently attached to the oligonucleotide. Preferred synthetic internucleoside linkages are phosphorothioates, alkylphosphonates, phosphorodithioates, phosphate esters,  
15 alkylphosphonothioates, phosphoramidates, carbamates, carbonates, phosphate triesters, acetamides, carboxymethyl esters and peptides.

The term "modified oligonucleotide" also encompasses oligonucleotides with a covalently modified base and/or sugar. For example, modified oligonucleotides include oligonucleotides having backbone sugars which are covalently attached to low molecular weight organic groups other  
20 than a hydroxyl group at the 3' position and other than a phosphate group at the 5' position. Thus modified oligonucleotides may include a 2'-O-alkylated ribose group. In addition, modified oligonucleotides may include sugars such as arabinose instead of ribose. The present invention, thus, contemplates pharmaceutical preparations containing modified antisense molecules that are complementary to and hybridizable with, under physiological conditions, nucleic acids encoding  
25 breast cancer associated antigen polypeptides, together with pharmaceutically acceptable carriers.

Antisense oligonucleotides may be administered as part of a pharmaceutical composition. Such a pharmaceutical composition may include the antisense oligonucleotides in combination with any standard physiologically and/or pharmaceutically acceptable carriers which are known in the art. The compositions should be sterile and contain a therapeutically effective amount of the antisense  
30 oligonucleotides in a unit of weight or volume suitable for administration to a patient. The term

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“pharmaceutically acceptable” means a non-toxic material that does not interfere with the effectiveness of the biological activity of the active ingredients. The term “physiologically acceptable” refers to a non-toxic material that is compatible with a biological system such as a cell, cell culture, tissue, or organism. The characteristics of the carrier will depend on the route of administration. Physiologically and pharmaceutically acceptable carriers include diluents, fillers, salts, buffers, stabilizers, solubilizers, and other materials which are well known in the art, as further described below.

As used herein, a “vector” may be any of a number of nucleic acids into which a desired sequence may be inserted by restriction and ligation for transport between different genetic environments or for expression in a host cell. Vectors are typically composed of DNA although RNA vectors are also available. Vectors include, but are not limited to, plasmids, phagemids and virus genomes. A cloning vector is one which is able to replicate in a host cell, and which is further characterized by one or more endonuclease restriction sites at which the vector may be cut in a determinable fashion and into which a desired DNA sequence may be ligated such that the new recombinant vector retains its ability to replicate in the host cell. In the case of plasmids, replication of the desired sequence may occur many times as the plasmid increases in copy number within the host bacterium or just a single time per host before the host reproduces by mitosis. In the case of phage, replication may occur actively during a lytic phase or passively during a lysogenic phase. An expression vector is one into which a desired DNA sequence may be inserted by restriction and ligation such that it is operably joined to regulatory sequences and may be expressed as an RNA transcript. Vectors may further contain one or more marker sequences suitable for use in the identification of cells which have or have not been transformed or transfected with the vector. Markers include, for example, genes encoding proteins which increase or decrease either resistance or sensitivity to antibiotics or other compounds, genes which encode enzymes whose activities are detectable by standard assays known in the art (e.g.,  $\beta$ -galactosidase or alkaline phosphatase), and genes which visibly affect the phenotype of transformed or transfected cells, hosts, colonies or plaques (e.g., green fluorescent protein). Preferred vectors are those capable of autonomous replication and expression of the structural gene products present in the DNA segments to which they are operably joined.

As used herein, a coding sequence and regulatory sequences are said to be “operably” joined

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when they are covalently linked in such a way as to place the expression or transcription of the coding sequence under the influence or control of the regulatory sequences. If it is desired that the coding sequences be translated into a functional protein, two DNA sequences are said to be operably joined if induction of a promoter in the 5' regulatory sequences results in the transcription of the coding sequence and if the nature of the linkage between the two DNA sequences does not (1) result in the introduction of a frame-shift mutation, (2) interfere with the ability of the promoter region to direct the transcription of the coding sequences, or (3) interfere with the ability of the corresponding RNA transcript to be translated into a protein. Thus, a promoter region would be operably joined to a coding sequence if the promoter region were capable of effecting transcription of that DNA sequence such that the resulting transcript might be translated into the desired protein or polypeptide.

The precise nature of the regulatory sequences needed for gene expression may vary between species or cell types, but shall in general include, as necessary, 5' non-transcribed and 5' non-translated sequences involved with the initiation of transcription and translation respectively, such as a TATA box, capping sequence, CAAT sequence, and the like. Especially, such 5' non-transcribed regulatory sequences will include a promoter region which includes a promoter sequence for transcriptional control of the operably joined gene. Regulatory sequences may also include enhancer sequences or upstream activator sequences as desired. The vectors of the invention may optionally include 5' leader or signal sequences. The choice and design of an appropriate vector is within the ability and discretion of one of ordinary skill in the art.

Expression vectors containing all the necessary elements for expression are commercially available and known to those skilled in the art. See, e.g., Sambrook et al., *Molecular Cloning: A Laboratory Manual*, Second Edition, Cold Spring Harbor Laboratory Press, 1989. Cells are genetically engineered by the introduction into the cells of heterologous DNA (RNA) encoding a breast cancer associated antigen polypeptide or fragment or variant thereof. That heterologous DNA (RNA) is placed under operable control of transcriptional elements to permit the expression of the heterologous DNA in the host cell.

Preferred systems for mRNA expression in mammalian cells are those such as pRc/CMV (available from Invitrogen, Carlsbad, CA) that contain a selectable marker such as a gene that confers G418 resistance (which facilitates the selection of stably transfected cell lines) and the

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human cytomegalovirus (CMV) enhancer-promoter sequences. Additionally, suitable for expression in primate or canine cell lines is the pCEP4 vector (Invitrogen), which contains an Epstein Barr Virus (EBV) origin of replication, facilitating the maintenance of plasmid as a multicopy extrachromosomal element. Another expression vector is the pEF-BOS plasmid containing the promoter of polypeptide Elongation Factor 1 $\alpha$ , which stimulates efficiently transcription *in vitro*. The plasmid is described by Mishizuma and Nagata (*Nuc. Acids Res.* 18:5322, 1990), and its use in transfection experiments is disclosed by, for example, Demoulin (*Mol. Cell. Biol.* 16:4710-4716, 1996). Still another preferred expression vector is an adenovirus, described by Stratford-Perricaudet, which is defective for E1 and E3 proteins (*J. Clin. Invest.* 90:626-630, 1992). The use of the adenovirus as an Adeno.P1A recombinant for the expression of an antigen is disclosed by Warnier et al., in intradermal injection in mice for immunization against P1A (*Int. J. Cancer*, 67:303-310, 1996). Additional vectors for delivery of nucleic acid are provided below.

The invention also embraces so-called expression kits, which allow the artisan to prepare a desired expression vector or vectors. Such expression kits include at least separate portions of a vector and one or more of the previously discussed breast cancer associated antigen nucleic acid molecules. Other components may be added, as desired, as long as the previously mentioned nucleic acid molecules, which are required, are included. The invention also includes kits for amplification of a breast cancer associated antigen nucleic acid, including at least one pair of amplification primers which hybridize to a breast cancer associated antigen nucleic acid. The primers preferably are 12-32 nucleotides in length and are non-overlapping to prevent formation of "primer-dimers". One of the primers will hybridize to one strand of the breast cancer associated antigen nucleic acid and the second primer will hybridize to the complementary strand of the breast cancer associated antigen nucleic acid, in an arrangement which permits amplification of the breast cancer associated antigen nucleic acid. Selection of appropriate primer pairs is standard in the art. For example, the selection can be made with assistance of a computer program designed for such a purpose, optionally followed by testing the primers for amplification specificity and efficiency.

The invention also permits the construction of cancer associated antigen gene "knock-outs" in cells and in animals, providing materials for studying certain aspects of cancer and immune system responses to cancer.

The invention also provides isolated polypeptides (including whole proteins and partial

proteins) encoded by the foregoing cancer associated antigen nucleic acids. Such polypeptides are useful, for example, alone or as fusion proteins to generate antibodies, as components of an immunoassay or diagnostic assay or as therapeutics. Cancer associated antigen polypeptides can be isolated from biological samples including tissue or cell homogenates, and can also be expressed  
5 recombinantly in a variety of prokaryotic and eukaryotic expression systems by constructing an expression vector appropriate to the expression system, introducing the expression vector into the expression system, and isolating the recombinantly expressed protein. Short polypeptides, including antigenic peptides (such as are presented by MHC molecules on the surface of a cell for immune recognition) also can be synthesized chemically using well-established methods of peptide synthesis.

10 A unique fragment of a cancer associated antigen polypeptide, in general, has the features and characteristics of unique fragments as discussed above in connection with nucleic acids. As will be recognized by those skilled in the art, the size of the unique fragment will depend upon factors such as whether the fragment constitutes a portion of a conserved protein domain. Thus, some regions of breast cancer associated antigens will require longer segments to be unique while others  
15 will require only short segments, typically between 5 and 12 amino acids (e.g. 5, 6, 7, 8, 9, 10, 11 or 12 or more, including each integer up to the full length, amino acids long).

Unique fragments of a polypeptide preferably are those fragments which retain a distinct functional capability of the polypeptide. Functional capabilities which can be retained in a unique fragment of a polypeptide include interaction with antibodies, interaction with other polypeptides or  
20 fragments thereof, selective binding of nucleic acids or proteins, and enzymatic activity. One important activity is the ability to act as a signature for identifying the polypeptide. Another is the ability to complex with HLA and to provoke in a human an immune response. Those skilled in the art are well versed in methods for selecting unique amino acid sequences, typically on the basis of the ability of the unique fragment to selectively distinguish the sequence of interest from non-family  
25 members. A comparison of the sequence of the fragment to those on known databases typically is all that is necessary.

The invention embraces variants of the cancer associated antigen polypeptides described above. As used herein, a "variant" of a cancer associated antigen polypeptide is a polypeptide which contains one or more modifications to the primary amino acid sequence of a cancer associated  
30 antigen polypeptide. Modifications which create a cancer associated antigen variant can be made to

a cancer associated antigen polypeptide 1) to reduce or eliminate an activity of a cancer associated antigen polypeptide; 2) to enhance a property of a cancer associated antigen polypeptide, such as protein stability in an expression system or the stability of protein-protein binding; 3) to provide a novel activity or property to a cancer associated antigen polypeptide, such as addition of an antigenic epitope or addition of a detectable moiety; or 4) to provide equivalent or better binding to an HLA molecule. Modifications to a cancer associated antigen polypeptide are typically made to the nucleic acid which encodes the cancer associated antigen polypeptide, and can include deletions, point mutations, truncations, amino acid substitutions and additions of amino acids or non-amino acid moieties. Alternatively, modifications can be made directly to the polypeptide, such as by cleavage, addition of a linker molecule, addition of a detectable moiety, such as biotin, addition of a fatty acid, and the like. Modifications also embrace fusion proteins comprising all or part of the cancer associated antigen amino acid sequence. One of skill in the art will be familiar with methods for predicting the effect on protein conformation of a change in protein sequence, and can thus "design" a variant cancer associated antigen polypeptide according to known methods. One example of such a method is described by Dahiyat and Mayo in *Science* 278:82-87, 1997, whereby proteins can be designed *de novo*. The method can be applied to a known protein to vary a only a portion of the polypeptide sequence. By applying the computational methods of Dahiyat and Mayo, specific variants of a cancer associated antigen polypeptide can be proposed and tested to determine whether the variant retains a desired conformation.

In general, variants include cancer associated antigen polypeptides which are modified specifically to alter a feature of the polypeptide unrelated to its desired physiological activity. For example, cysteine residues can be substituted or deleted to prevent unwanted disulfide linkages. Similarly, certain amino acids can be changed to enhance expression of a breast cancer associated antigen polypeptide by eliminating proteolysis by proteases in an expression system (e.g., dibasic amino acid residues in yeast expression systems in which KEX2 protease activity is present).

Mutations of a nucleic acid which encode a cancer associated antigen polypeptide preferably preserve the amino acid reading frame of the coding sequence, and preferably do not create regions in the nucleic acid which are likely to hybridize to form secondary structures, such a hairpins or loops, which can be deleterious to expression of the variant polypeptide.

Mutations can be made by selecting an amino acid substitution, or by random mutagenesis of

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a selected site in a nucleic acid which encodes the polypeptide. Variant polypeptides are then expressed and tested for one or more activities to determine which mutation provides a variant polypeptide with the desired properties. Further mutations can be made to variants (or to non-variant cancer associated antigen polypeptides) which are silent as to the amino acid sequence of the polypeptide, but which provide preferred codons for translation in a particular host. The preferred codons for translation of a nucleic acid in, e.g., *E. coli*, are well known to those of ordinary skill in the art. Still other mutations can be made to the noncoding sequences of a cancer associated antigen gene or cDNA clone to enhance expression of the polypeptide. The activity of variants of cancer associated antigen polypeptides can be tested by cloning the gene encoding the variant cancer associated antigen polypeptide into a bacterial or mammalian expression vector, introducing the vector into an appropriate host cell, expressing the variant cancer associated antigen polypeptide, and testing for a functional capability of the cancer associated antigen polypeptides as disclosed herein. For example, the variant cancer associated antigen polypeptide can be tested for reaction with autologous or allogeneic sera as disclosed in the Examples. Preparation of other variant polypeptides may favor testing of other activities, as will be known to one of ordinary skill in the art.

The skilled artisan will also realize that conservative amino acid substitutions may be made in cancer associated antigen polypeptides to provide functionally equivalent variants of the foregoing polypeptides, i.e., the variants retain the functional capabilities of the cancer associated antigen polypeptides. As used herein, a "conservative amino acid substitution" refers to an amino acid substitution which does not alter the relative charge or size characteristics of the protein in which the amino acid substitution is made. Variants can be prepared according to methods for altering polypeptide sequence known to one of ordinary skill in the art such as are found in references which compile such methods, e.g., *Molecular Cloning: A Laboratory Manual*, J. Sambrook, et al., eds., Second Edition, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, New York, 1989, or *Current Protocols in Molecular Biology*, F.M. Ausubel, et al., eds., John Wiley & Sons, Inc., New York. Exemplary functionally equivalent variants of the cancer associated antigen polypeptides include conservative amino acid substitutions of in the amino acid sequences of SEQ ID proteins disclosed herein. Conservative substitutions of amino acids include substitutions made amongst amino acids within the following groups: (a) M, I, L, V; (b) F, Y, W; (c) K, R, H; (d) A, G; (e) S, T; (f) Q, N; and (g) E, D.



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For example, upon determining that a peptide derived from a cancer associated antigen polypeptide is presented by an MHC molecule and recognized by CTLs (e.g., as described in the Examples), one can make conservative amino acid substitutions to the amino acid sequence of the peptide, particularly at residues which are thought not to be direct contact points with the MHC molecule. For example, methods for identifying functional variants of HLA class II binding peptides are provided in a published PCT application of Strominger and Wucherpfennig (PCT/US96/03182). Peptides bearing one or more amino acid substitutions also can be tested for concordance with known HLA/MHC motifs prior to synthesis using, e.g. the computer program described by D'Amaro and Drijfhout (D'Amaro et al., *Human Immunol.* 43:13-18, 1995; Drijfhout et al., *Human Immunol.* 43:1-12, 1995). The substituted peptides can then be tested for binding to the MHC molecule and recognition by CTLs when bound to MHC. These variants can be tested for improved stability and are useful, *inter alia*, in vaccine compositions.

Conservative amino-acid substitutions in the amino acid sequence of cancer associated antigen polypeptides to produce functionally equivalent variants of cancer associated antigen polypeptides typically are made by alteration of a nucleic acid encoding a cancer associated antigen polypeptide. Such substitutions can be made by a variety of methods known to one of ordinary skill in the art. For example, amino acid substitutions may be made by PCR-directed mutation, site-directed mutagenesis according to the method of Kunkel (Kunkel, *Proc. Nat. Acad. Sci. U.S.A.* 82: 488-492, 1985), or by chemical synthesis of a gene encoding a cancer associated antigen polypeptide. Where amino acid substitutions are made to a small unique fragment of a cancer associated antigen polypeptide, such as an antigenic epitope recognized by autologous or allogeneic sera or cytolytic T lymphocytes, the substitutions can be made by directly synthesizing the peptide. The activity of functionally equivalent fragments of cancer associated antigen polypeptides can be tested by cloning the gene encoding the altered cancer associated antigen polypeptide into a bacterial or mammalian expression vector, introducing the vector into an appropriate host cell, expressing the altered cancer associated antigen polypeptide, and testing for a functional capability of the cancer associated antigen polypeptides as disclosed herein. Peptides which are chemically synthesized can be tested directly for function, e.g., for binding to antisera recognizing associated antigens.

The invention as described herein has a number of uses, some of which are described elsewhere herein. First, the invention permits isolation of the cancer associated antigen protein

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molecules. A variety of methodologies well-known to the skilled practitioner can be utilized to obtain isolated cancer associated antigen molecules. The polypeptide may be purified from cells which naturally produce the polypeptide by chromatographic means or immunological recognition. Alternatively, an expression vector may be introduced into cells to cause production of the polypeptide. In another method, mRNA transcripts may be microinjected or otherwise introduced into cells to cause production of the encoded polypeptide. Translation of mRNA in cell-free extracts such as the reticulocyte lysate system also may be used to produce polypeptide. Those skilled in the art also can readily follow known methods for isolating cancer associated antigen polypeptides. These include, but are not limited to, immunochromatography, HPLC, size-exclusion chromatography, ion-exchange chromatography and immune-affinity chromatography.

The isolation and identification of cancer associated antigen genes also makes it possible for the artisan to diagnose a disorder characterized by expression of cancer associated antigens. These methods involve determining expression of one or more cancer associated antigen nucleic acids, and/or encoded cancer associated antigen polypeptides and/or peptides derived therefrom. In the former situation, such determinations can be carried out via any standard nucleic acid determination assay, including the polymerase chain reaction, or assaying with labeled hybridization probes. In the latter situation, such determinations can be carried out by screening patient antisera for recognition of the polypeptide.

The invention also makes it possible isolate proteins which bind to cancer associated antigens as disclosed herein, including antibodies and cellular binding partners of the cancer associated antigens. Additional uses are described further herein.

The invention also provides, in certain embodiments, "dominant negative" polypeptides derived from cancer associated antigen polypeptides. A dominant negative polypeptide is an inactive variant of a protein, which, by interacting with the cellular machinery, displaces an active protein from its interaction with the cellular machinery or competes with the active protein, thereby reducing the effect of the active protein. For example, a dominant negative receptor which binds a ligand but does not transmit a signal in response to binding of the ligand can reduce the biological effect of expression of the ligand. Likewise, a dominant negative catalytically-inactive kinase which interacts normally with target proteins but does not phosphorylate the target proteins can reduce phosphorylation of the target proteins in response to a cellular signal. Similarly, a dominant

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negative transcription factor which binds to a promoter site in the control region of a gene but does not increase gene transcription can reduce the effect of a normal transcription factor by occupying promoter binding sites without increasing transcription.

The end result of the expression of a dominant negative polypeptide in a cell is a reduction in function of active proteins. One of ordinary skill in the art can assess the potential for a dominant negative variant of a protein, and using standard mutagenesis techniques to create one or more dominant negative variant polypeptides. For example, given the teachings contained herein of cancer associated antigens, especially those which are similar to known proteins which have known activities, one of ordinary skill in the art can modify the sequence of the cancer associated antigens by site-specific mutagenesis, scanning mutagenesis, partial gene deletion or truncation, and the like. See, e.g., U.S. Patent No. 5,580,723 and Sambrook et al., *Molecular Cloning: A Laboratory Manual*, Second Edition, Cold Spring Harbor Laboratory Press, 1989. The skilled artisan then can test the population of mutagenized polypeptides for diminution in a selected and/or for retention of such an activity. Other similar methods for creating and testing dominant negative variants of a protein will be apparent to one of ordinary skill in the art.

The invention also involves agents such as polypeptides which bind to cancer associated antigen polypeptides. Such binding agents can be used, for example, in screening assays to detect the presence or absence of cancer associated antigen polypeptides and complexes of cancer associated antigen polypeptides and their binding partners and in purification protocols to isolated cancer associated antigen polypeptides and complexes of cancer associated antigen polypeptides and their binding partners. Such agents also can be used to inhibit the native activity of the cancer associated antigen polypeptides, for example, by binding to such polypeptides.

The invention, therefore, embraces peptide binding agents which, for example, can be antibodies or fragments of antibodies having the ability to selectively bind to cancer associated antigen polypeptides. Antibodies include polyclonal and monoclonal antibodies, prepared according to conventional methodology.

Significantly, as is well-known in the art, only a small portion of an antibody molecule, the paratope, is involved in the binding of the antibody to its epitope (see, in general, Clark, W.R. (1986) The Experimental Foundations of Modern Immunology Wiley & Sons, Inc., New York; Roitt, I. (1991) Essential Immunology, 7th Ed., Blackwell Scientific Publications, Oxford). The

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pFc' and Fc regions, for example, are effectors of the complement cascade but are not involved in antigen binding. An antibody from which the pFc' region has been enzymatically cleaved, or which has been produced without the pFc' region, designated an F(ab')<sub>2</sub> fragment, retains both of the antigen binding sites of an intact antibody. Similarly, an antibody from which the Fc region has been enzymatically cleaved, or which has been produced without the Fc region, designated an Fab fragment, retains one of the antigen binding sites of an intact antibody molecule. Proceeding further, Fab fragments consist of a covalently bound antibody light chain and a portion of the antibody heavy chain denoted Fd. The Fd fragments are the major determinant of antibody specificity (a single Fd fragment may be associated with up to ten different light chains without altering antibody specificity) and Fd fragments retain epitope-binding ability in isolation.

Within the antigen-binding portion of an antibody, as is well-known in the art, there are complementarity determining regions (CDRs), which directly interact with the epitope of the antigen, and framework regions (FRs), which maintain the tertiary structure of the paratope (see, in general, Clark, 1986; Roitt, 1991). In both the heavy chain Fd fragment and the light chain of IgG immunoglobulins, there are four framework regions (FR1 through FR4) separated respectively by three complementarity determining regions (CDR1 through CDR3). The CDRs, and in particular the CDR3 regions, and more particularly the heavy chain CDR3, are largely responsible for antibody specificity.

It is now well-established in the art that the non-CDR regions of a mammalian antibody may be replaced with similar regions of conspecific or heterospecific antibodies while retaining the epitopic specificity of the original antibody. This is most clearly manifested in the development and use of "humanized" antibodies in which non-human CDRs are covalently joined to human FR and/or Fc/pFc' regions to produce a functional antibody. Thus, for example, PCT International Publication Number WO 92/04381 teaches the production and use of humanized murine RSV antibodies in which at least a portion of the murine FR regions have been replaced by FR regions of human origin. Such antibodies, including fragments of intact antibodies with antigen-binding ability, are often referred to as "chimeric" antibodies.

Thus, as will be apparent to one of ordinary skill in the art, the present invention also provides for F(ab')<sub>2</sub>, Fab, Fv and Fd fragments; chimeric antibodies in which the Fc and/or FR and/or CDR1 and/or CDR2 and/or light chain CDR3 regions have been replaced by homologous

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human or non-human sequences; chimeric F(ab')<sub>2</sub> fragment antibodies in which the FR and/or CDR1 and/or CDR2 and/or light chain CDR3 regions have been replaced by homologous human or non-human sequences; chimeric Fab fragment antibodies in which the FR and/or CDR1 and/or CDR2 and/or light chain CDR3 regions have been replaced by homologous human or non-human sequences; and chimeric Fd fragment antibodies in which the FR and/or CDR1 and/or CDR2 regions have been replaced by homologous human or non-human sequences. The present invention also includes so-called single chain antibodies.

Thus, the invention involves polypeptides of numerous size and type that bind specifically to cancer associated antigen polypeptides, and complexes of both cancer associated antigen polypeptides and their binding partners. These polypeptides may be derived also from sources other than antibody technology. For example, such polypeptide binding agents can be provided by degenerate peptide libraries which can be readily prepared in solution, in immobilized form or as phage display libraries. Combinatorial libraries also can be synthesized of peptides containing one or more amino acids. Libraries further can be synthesized of peptoids and non-peptide synthetic moieties.

Phage display can be particularly effective in identifying binding peptides useful according to the invention. Briefly, one prepares a phage library (using e.g. m13, fd, or lambda phage), displaying inserts from 4 to about 80 amino acid residues using conventional procedures. The inserts may represent, for example, a completely degenerate or biased array. One then can select phage-bearing inserts which bind to the cancer associated antigen polypeptide. This process can be repeated through several cycles of reselection of phage that bind to the cancer associated antigen polypeptide. Repeated rounds lead to enrichment of phage bearing particular sequences. DNA sequence analysis can be conducted to identify the sequences of the expressed polypeptides. The minimal linear portion of the sequence that binds to the cancer associated antigen polypeptide can be determined. One can repeat the procedure using a biased library containing inserts containing part or all of the minimal linear portion plus one or more additional degenerate residues upstream or downstream thereof. Yeast two-hybrid screening methods also may be used to identify polypeptides that bind to the cancer associated antigen polypeptides. Thus, the cancer associated antigen polypeptides of the invention, or a fragment thereof, can be used to screen peptide libraries, including phage display libraries, to identify and select peptide binding partners of the cancer

associated antigen polypeptides of the invention. Such molecules can be used, as described, for screening assays, for purification protocols, for interfering directly with the functioning of cancer associated antigen and for other purposes that will be apparent to those of ordinary skill in the art.

As detailed herein, the foregoing antibodies and other binding molecules may be used for example to identify tissues expressing protein or to purify protein. Antibodies also may be coupled to specific diagnostic labeling agents for imaging of cells and tissues that express cancer associated antigens or to therapeutically useful agents according to standard coupling procedures. Diagnostic agents include, but are not limited to, barium sulfate, iocetamic acid, iopanoic acid, ipodate calcium, diatrizoate sodium, diatrizoate meglumine, metrizamide, tyropanoate sodium and radiodiagnostics including positron emitters such as fluorine-18 and carbon-11, gamma emitters such as iodine-123, technetium-99m, iodine-131 and indium-111, nuclides for nuclear magnetic resonance such as fluorine and gadolinium. Other diagnostic agents useful in the invention will be apparent to one of ordinary skill in the art. As used herein, "therapeutically useful agents" include any therapeutic molecule which desirably is targeted selectively to a cell expressing one of the cancer antigens disclosed herein, including antineoplastic agents, radioiodinated compounds, toxins, other cytostatic or cytolytic drugs, and so forth. Antineoplastic therapeutics are well known and include: aminoglutethimide, azathioprine, bleomycin sulfate, busulfan, carmustine, chlorambucil, cisplatin, cyclophosphamide, cyclosporine, cytarabidine, dacarbazine, dactinomycin, daunorubicin, doxorubicin, taxol, etoposide, fluorouracil, interferon- $\alpha$ , lomustine, mercaptopurine, methotrexate, mitotane, procarbazine HCl, thioguanine, vinblastine sulfate and vincristine sulfate. Additional antineoplastic agents include those disclosed in Chapter 52, Antineoplastic Agents (Paul Calabresi and Bruce A. Chabner), and the introduction thereto, 1202-1263, of Goodman and Gilman's "The Pharmacological Basis of Therapeutics", Eighth Edition, 1990, McGraw-Hill, Inc. (Health Professions Division). Toxins can be proteins such as, for example, pokeweed anti-viral protein, cholera toxin, pertussis toxin, ricin, gelonin, abrin, diphtheria exotoxin, or *Pseudomonas* exotoxin. Toxin moieties can also be high energy-emitting radionuclides such as cobalt-60.

In the foregoing methods, antibodies prepared according to the invention also preferably are specific for the cancer associated antigen/MHC complexes described herein.

When "disorder" is used herein, it refers to any pathological condition where the cancer associated antigens are expressed. An example of such a disorder is cancer, breast, colon, gastric,

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renal, prostate and lung cancers as particular examples.

Samples of tissue and/or cells for use in the various methods described herein can be obtained through standard methods such as tissue biopsy, including punch biopsy and cell scraping, and collection of blood or other bodily fluids by aspiration or other methods.

5 In certain embodiments of the invention, an immunoreactive cell sample is removed from a subject. By "immunoreactive cell" is meant a cell which can mature into an immune cell (such as a B cell, a helper T cell, or a cytolytic T cell) upon appropriate stimulation. Thus immunoreactive cells include CD34<sup>+</sup> hematopoietic stem cells, immature T cells and immature B cells. When it is desired to produce cytolytic T cells which recognize a cancer associated antigen, the  
10 immunoreactive cell is contacted with a cell which expresses a cancer associated antigen under conditions favoring production, differentiation and/or selection of cytolytic T cells; the differentiation of the T cell precursor into a cytolytic T cell upon exposure to antigen is similar to clonal selection of the immune system.

Some therapeutic approaches based upon the disclosure are premised on a response by a  
15 subject's immune system, leading to lysis of antigen presenting cells, such as breast cancer cells which present one or more cancer associated antigens. One such approach is the administration of autologous CTLs specific to a cancer associated antigen/MHC complex to a subject with abnormal cells of the phenotype at issue. It is within the ability of one of ordinary skill in the art to develop such CTLs *in vitro*. An example of a method for T cell differentiation is presented in International  
20 Application number PCT/US96/05607. Generally, a sample of cells taken from a subject, such as blood cells, are contacted with a cell presenting the complex and capable of provoking CTLs to proliferate. The target cell can be a transfectant, such as a COS cell of the type described herein. These transfectants present the desired complex of their surface and, when combined with a CTL of interest, stimulate its proliferation. COS cells, such as those used herein are widely available, as are  
25 other suitable host cells. Specific production of a CTL clone is described herein, and is well known in the art. The clonally expanded autologous CTLs then are administered to the subject.

Another method for selecting antigen-specific CTL clones has recently been described (Altman et al., *Science* 274:94-96, 1996; Dunbar et al., *Curr. Biol.* 8:413-416, 1998), in which fluorogenic tetramers of MHC class I molecule/peptide complexes are used to detect specific CTL  
30 clones. Briefly, soluble MHC class I molecules are folded *in vitro* in the presence of  $\beta_2$ -

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microglobulin and a peptide antigen which binds the class I molecule. After purification, the MHC/peptide complex is purified and labeled with biotin. Tetramers are formed by mixing the biotinylated peptide-MHC complex with labeled avidin (e.g. phycoerythrin) at a molar ratio of 4:1. Tetramers are then contacted with a source of CTLs such as peripheral blood or lymph node. The tetramers bind CTLs which recognize the peptide antigen/MHC class I complex. Cells bound by the tetramers can be sorted by fluorescence activated cell sorting to isolate the reactive CTLs. The isolated CTLs then can be expanded *in vitro* for use as described herein.

To detail a therapeutic methodology, referred to as adoptive transfer (Greenberg, *J. Immunol.* 136(5): 1917, 1986; Riddel et al., *Science* 257: 238, 1992; Lynch et al, *Eur. J. Immunol.* 21: 1403-1410, 1991; Kast et al., *Cell* 59: 603-614, 1989), cells presenting the desired complex are combined with CTLs leading to proliferation of the CTLs specific thereto. The proliferated CTLs are then administered to a subject with a cellular abnormality which is characterized by certain of the abnormal cells presenting the particular complex. The CTLs then lyse the abnormal cells, thereby achieving the desired therapeutic goal.

The foregoing therapy assumes that at least some of the subject's abnormal cells present the relevant HLA cancer associated antigen complex. This can be determined very easily, as the art is very familiar with methods for identifying cells which present a particular HLA molecule, as well as how to identify cells expressing DNA of the pertinent sequences, in this case a cancer associated antigen sequence. Once cells presenting the relevant complex are identified via the foregoing screening methodology, they can be combined with a sample from a patient, where the sample contains CTLs. If the complex presenting cells are lysed by the mixed CTL sample, then it can be assumed that a cancer associated antigen is being presented, and the subject is an appropriate candidate for the therapeutic approaches set forth *supra*.

Adoptive transfer is not the only form of therapy that is available in accordance with the invention. CTLs can also be provoked *in vivo*, using a number of approaches. One approach is the use of non-proliferative cells expressing the complex. The cells used in this approach may be those that normally express the complex, such as irradiated tumor cells or cells transfected with one or both of the genes necessary for presentation of the complex (i.e. the antigenic peptide and the presenting HLA molecule). Chen et al. (*Proc. Natl. Acad. Sci. USA* 88: 110-114, 1991) exemplifies this approach, showing the use of transfected cells expressing HPV E7 peptides in a therapeutic



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regime. Various cell types may be used. Similarly, vectors carrying one or both of the genes of interest may be used. Viral or bacterial vectors are especially preferred. For example, nucleic acids which encode a breast cancer associated antigen polypeptide or peptide may be operably linked to promoter and enhancer sequences which direct expression of the cancer associated antigen polypeptide or peptide in certain tissues or cell types. The nucleic acid may be incorporated into an expression vector. Expression vectors may be unmodified extrachromosomal nucleic acids, plasmids or viral genomes constructed or modified to enable insertion of exogenous nucleic acids, such as those encoding cancer associated antigen, as described elsewhere herein. Nucleic acids encoding a cancer associated antigen also may be inserted into a retroviral genome, thereby facilitating integration of the nucleic acid into the genome of the target tissue or cell type. In these systems, the gene of interest is carried by a microorganism, e.g., a Vaccinia virus, retrovirus or adenovirus, and the materials de facto "infect" host cells. The cells which result present the complex of interest, and are recognized by autologous CTLs, which then proliferate.

A similar effect can be achieved by combining the cancer associated antigen or a stimulatory fragment thereof with an adjuvant to facilitate incorporation into antigen presenting cells *in vivo*. The breast cancer associated antigen polypeptide is processed to yield the peptide partner of the HLA molecule while a cancer associated antigen peptide may be presented without the need for further processing. Generally, subjects can receive an intradermal injection of an effective amount of the cancer associated antigen. Initial doses can be followed by booster doses, following immunization protocols standard in the art. Preferred cancer associated antigens include those found to react with allogeneic cancer antisera, such as the nucleic acids (and encoded polypeptides and peptides) of SEQ ID NO:31,33 and 34 and others, for example, shown in the examples below.

The invention involves the use of various materials disclosed herein to "immunize" subjects or as "vaccines". As used herein, "immunization" or "vaccination" means increasing or activating an immune response against an antigen. It does not require elimination or eradication of a condition but rather contemplates the clinically favorable enhancement of an immune response toward an antigen. Generally accepted animal models can be used for testing of immunization against breast cancer using a cancer associated antigen nucleic acid. For example, cancer cells can be introduced into a mouse to create a tumor, and one or more cancer associated antigen nucleic acids can be delivered by the methods described herein. The effect on the cancer cells (e.g., reduction of tumor

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size) can be assessed as a measure of the effectiveness of the cancer associated antigen nucleic acid immunization. Of course, testing of the foregoing animal model using more conventional methods for immunization include the administration of one or more cancer associated antigen polypeptides or peptides derived therefrom, optionally combined with one or more adjuvants and/or cytokines to boost the immune response. Methods for immunization, including formulation of a vaccine composition and selection of doses, route of administration and the schedule of administration (e.g. primary and one or more booster doses), are well known in the art. The tests also can be performed in humans, where the end point is to test for the presence of enhanced levels of circulating CTLs against cells bearing the antigen, to test for levels of circulating antibodies against the antigen, to test for the presence of cells expressing the antigen and so forth.

As part of the immunization compositions, one or more cancer associated antigens or stimulatory fragments thereof are administered with one or more adjuvants to induce an immune response or to increase an immune response. An adjuvant is a substance incorporated into or administered with antigen which potentiates the immune response. Adjuvants may enhance the immunological response by providing a reservoir of antigen (extracellularly or within macrophages), activating macrophages and stimulating specific sets of lymphocytes. Adjuvants of many kinds are well known in the art. Specific examples of adjuvants include monophosphoryl lipid A (MPL, SmithKline Beecham), a congener obtained after purification and acid hydrolysis of *Salmonella minnesota* Re 595 lipopolysaccharide; saponins including QS21 (SmithKline Beecham), a pure QA-21 saponin purified from *Quillja saponaria* extract; DQS21, described in PCT application WO96/33739 (SmithKline Beecham); QS-7, QS-17, QS-18, and QS-L1 (So et al., *Mol. Cells* 7:178-186, 1997); incomplete Freund's adjuvant; complete Freund's adjuvant; montanide; and various water-in-oil emulsions prepared from biodegradable oils such as squalene and/or tocopherol. Preferably, the peptides are administered mixed with a combination of DQS21/MPL. The ratio of DQS21 to MPL typically will be about 1:10 to 10:1, preferably about 1:5 to 5:1 and more preferably about 1:1. Typically for human administration, DQS21 and MPL will be present in a vaccine formulation in the range of about 1 µg to about 100 µg. Other adjuvants are known in the art and can be used in the invention (see, e.g. Goding, *Monoclonal Antibodies: Principles and Practice*, 2nd Ed., 1986). Methods for the preparation of mixtures or emulsions of peptide and adjuvant are well known to those of skill in the art of vaccination.

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Other agents which stimulate the immune response of the subject can also be administered to the subject. For example, other cytokines are also useful in vaccination protocols as a result of their lymphocyte regulatory properties. Many other cytokines useful for such purposes will be known to one of ordinary skill in the art, including interleukin-12 (IL-12) which has been shown to enhance the protective effects of vaccines (*see, e.g., Science* 268: 1432-1434, 1995), GM-CSF and IL-18. Thus cytokines can be administered in conjunction with antigens and adjuvants to increase the immune response to the antigens.

There are a number of immune response potentiating compounds that can be used in vaccination protocols. These include costimulatory molecules provided in either protein or nucleic acid form. Such costimulatory molecules include the B7-1 and B7-2 (CD80 and CD86 respectively) molecules which are expressed on dendritic cells (DC) and interact with the CD28 molecule expressed on the T cell. This interaction provides costimulation (signal 2) to an antigen/MHC/TCR stimulated (signal 1) T cell, increasing T cell proliferation and effector function. B7 also interacts with CTLA4 (CD152) on T cells and studies involving CTLA4 and B7 ligands indicate that the B7-CTLA4 interaction can enhance antitumor immunity and CTL proliferation, Zheng P., et al. *PNAS* 95 (11) 6284-6289 (1998).

B7 typically is not expressed on tumor cells so they are not efficient antigen presenting cells (APCs) for T cells. Induction of B7 expression would enable the tumor cells to stimulate more efficiently CTL proliferation and effector function. A combination of B7/IL-6/IL-12 costimulation has been shown to induce IFN-gamma and a Th1 cytokine profile in the T cell population leading to further enhanced T cell activity, Gajewski et al., *J. Immunol.*, 154:5637-5648 (1995). Tumor cell transfection with B7 has been discussed in relation to *in vitro* CTL expansion for adoptive transfer immunotherapy by Wang et al., *J Immunol*, 19:1-8 (1986). Other delivery mechanisms for the B7 molecule would include nucleic acid (naked DNA) immunization Kim J., et al. *Nat Biotechnol.*, 15:7:641-646 (1997) and recombinant viruses such as adeno and pox (Wendtner et al., *Gene Ther*, 4:7:726-735 (1997)). These systems are all amenable to the construction and use of expression cassettes for the coexpression of B7 with other molecules of choice such as the antigens or fragment(s) of antigens discussed herein (including polytopes) or cytokines. These delivery systems can be used for induction of the appropriate molecules *in vitro* and for *in vivo* vaccination situations. The use of anti-CD28 antibodies to directly stimulate T cells *in vitro* and *in vivo* could also be

considered.

Lymphocyte function associated antigen-3 (LFA-3) is expressed on APCs and some tumor cells and interacts with CD2 expressed on T cells. This interaction induces T cell IL-2 and IFN-gamma production and can thus complement but not substitute, the B7/CD28 costimulatory interaction, Parra et al., *J. Immunol.*, 158:637-642 (1997), Fenton et al., *J. Immunother*, 21:2:95-108 (1989).

Lymphocyte function associated antigen-1 (LFA-1) is expressed on leukocytes and interacts with ICAM-1 expressed on APCs and some tumor cells. This interaction induces T cell IL-2 and IFN-gamma production and can thus complement but not substitute, the B7/CD28 costimulatory interaction, Fenton et al., *J. Immunother*, 21:2:95-108 (1998). LFA-1 is thus a further example of a costimulatory molecule that could be provided in a vaccination protocol in the various ways discussed above for B7.

Complete CTL activation and effector function requires Th cell help through the interaction between the Th cell CD40L (CD40 ligand) molecule and the CD40 molecule expressed by DCS, Ridge et al., *Nature*, 393:474 (1998), Bennett et al., *Nature*, 393:478 (1998), Schoenberger et al., *Nature*, 393:480 (1998). This mechanism of this costimulatory signal is likely to involve upregulation of B7 and associated IL-6/IL-12 production by the DC (APC). The CD40-CD40L interaction thus complements the signal 1 (antigen/MHC-TCR) and signal 2 (B7-CD28) interactions.

The use of anti-CD40 antibodies to stimulate DC cells directly, would be expected to enhance a response to tumor antigens which are normally encountered outside of a inflammatory context or are presented by non-professional APCs (tumor cells). In these situations Th help and B7 costimulation signals are not provided. This mechanism might be used in the context of antigen pulsed DC based therapies or in situations where Th epitopes have not been defined within known TRA precursors.

A cancer associated antigen polypeptide, or a fragment thereof, also can be used to isolate their native binding partners. Isolation of such binding partners may be performed according to well-known methods. For example, isolated cancer associated antigen polypeptides can be attached to a substrate (e.g., chromatographic media, such as polystyrene beads, or a filter), and then a solution suspected of containing the binding partner may be applied to the substrate. If a binding partner which can interact with cancer associated antigen polypeptides is present in the solution,

then it will bind to the substrate-bound cancer associated antigen polypeptide. The binding partner then may be isolated.

It will also be recognized that the invention embraces the use of the cancer associated antigen cDNA sequences in expression vectors, as well as to transfect host cells and cell lines, be these  
5 prokaryotic (e.g., *E. coli*), or eukaryotic (e.g., dendritic cells, B cells, CHO cells, COS cells, yeast expression systems and recombinant baculovirus expression in insect cells). Especially useful are mammalian cells such as human, mouse, hamster, pig, goat, primate, etc. They may be of a wide variety of tissue types, and include primary cells and cell lines. Specific examples include keratinocytes, peripheral blood leukocytes, bone marrow stem cells and embryonic stem cells. The  
10 expression vectors require that the pertinent sequence, i.e., those nucleic acids described *supra*, be operably linked to a promoter.

The invention also contemplates delivery of nucleic acids, polypeptides or peptides for vaccination. Delivery of polypeptides and peptides can be accomplished according to standard vaccination protocols which are well known in the art. In another embodiment, the delivery of  
15 nucleic acid is accomplished by *ex vivo* methods, i.e. by removing a cell from a subject, genetically engineering the cell to include a breast cancer associated antigen, and reintroducing the engineered cell into the subject. One example of such a procedure is outlined in U.S. Patent 5,399,346 and in exhibits submitted in the file history of that patent, all of which are publicly available documents. In general, it involves introduction *in vitro* of a functional copy of a gene into a cell(s) of a subject, and  
20 returning the genetically engineered cell(s) to the subject. The functional copy of the gene is under operable control of regulatory elements which permit expression of the gene in the genetically engineered cell(s). Numerous transfection and transduction techniques as well as appropriate expression vectors are well known to those of ordinary skill in the art, some of which are described in PCT application WO95/00654. *In vivo* nucleic acid delivery using vectors such as viruses and  
25 targeted liposomes also is contemplated according to the invention.

In preferred embodiments, a virus vector for delivering a nucleic acid encoding a cancer associated antigen is selected from the group consisting of adenoviruses, adeno-associated viruses, poxviruses including vaccinia viruses and attenuated poxviruses, Semliki Forest virus, Venezuelan equine encephalitis virus, retroviruses, Sindbis virus, and Ty virus-like particle. Examples of  
30 viruses and virus-like particles which have been used to deliver exogenous nucleic acids include:

replication-defective adenoviruses (e.g., Xiang et al., *Virology* 219:220-227, 1996; Eloit et al., *J. Virol* 71:5375-5381, 1997; Chengalvala et al., *Vaccine* 15:335-339, 1997), a modified retrovirus (Townsend et al., *J. Virol.* 71:3365-3374, 1997), a nonreplicating retrovirus (Irwin et al., *J. Virol.* 68:5036-5044, 1994), a replication defective Semliki Forest virus (Zhao et al., *Proc. Natl. Acad. Sci. USA* 92:3009-3013, 1995), canarypox virus and highly attenuated vaccinia virus derivative (Paoletti, *Proc. Natl. Acad. Sci. USA* 93:11349-11353, 1996), non-replicative vaccinia virus (Moss, *Proc. Natl. Acad. Sci. USA* 93:11341-11348, 1996), replicative vaccinia virus (Moss, *Dev. Biol. Stand.* 82:55-63, 1994), Venezuelan equine encephalitis virus (Davis et al., *J. Virol.* 70:3781-3787, 1996), Sindbis virus (Pugachev et al., *Virology* 212:587-594, 1995), and Ty virus-like particle (Allsopp et al., *Eur J. Immunol* 26:1951-1959, 1996). In preferred embodiments, the virus vector is an adenovirus.

Another preferred virus for certain applications is the adeno-associated virus, a double-stranded DNA virus. The adeno-associated virus is capable of infecting a wide range of cell types and species and can be engineered to be replication-deficient. It further has advantages, such as heat and lipid solvent stability, high transduction frequencies in cells of diverse lineages, including hematopoietic cells, and lack of superinfection inhibition thus allowing multiple series of transductions. The adeno-associated virus can integrate into human cellular DNA in a site-specific manner, thereby minimizing the possibility of insertional mutagenesis and variability of inserted gene expression. In addition, wild-type adeno-associated virus infections have been followed in tissue culture for greater than 100 passages in the absence of selective pressure, implying that the adeno-associated virus genomic integration is a relatively stable event. The adeno-associated virus can also function in an extrachromosomal fashion.

In general, other preferred viral vectors are based on non-cytopathic eukaryotic viruses in which non-essential genes have been replaced with the gene of interest. Non-cytopathic viruses include retroviruses, the life cycle of which involves reverse transcription of genomic viral RNA into DNA with subsequent proviral integration into host cellular DNA. Adenoviruses and retroviruses have been approved for human gene therapy trials. In general, the retroviruses are replication-deficient (i.e., capable of directing synthesis of the desired proteins, but incapable of manufacturing an infectious particle). Such genetically altered retroviral expression vectors have general utility for the high-efficiency transduction of genes *in vivo*. Standard protocols for

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producing replication-deficient retroviruses (including the steps of incorporation of exogenous genetic material into a plasmid, transfection of a packaging cell lined with plasmid, production of recombinant retroviruses by the packaging cell line, collection of viral particles from tissue culture media, and infection of the target cells with viral particles) are provided in Kriegler, M., "Gene  
5 Transfer and Expression, A Laboratory Manual," W.H. Freeman C.O., New York (1990) and Murry, E.J. Ed. "Methods in Molecular Biology," vol. 7, Humana Press, Inc., Clifton, New Jersey (1991).

Preferably the foregoing nucleic acid delivery vectors: (1) contain exogenous genetic material that can be transcribed and translated in a mammalian cell and that can induce an immune response in a host, and (2) contain on a surface a ligand that selectively binds to a receptor on the  
10 surface of a target cell, such as a mammalian cell, and thereby gains entry to the target cell.

Various techniques may be employed for introducing nucleic acids of the invention into cells, depending on whether the nucleic acids are introduced *in vitro* or *in vivo* in a host. Such techniques include transfection of nucleic acid-CaPO<sub>4</sub> precipitates, transfection of nucleic acids associated with DEAE, transfection or infection with the foregoing viruses including the nucleic  
15 acid of interest, liposome mediated transfection, and the like. For certain uses, it is preferred to target the nucleic acid to particular cells. In such instances, a vehicle used for delivering a nucleic acid of the invention into a cell (e.g., a retrovirus, or other virus; a liposome) can have a targeting molecule attached thereto. For example, a molecule such as an antibody specific for a surface membrane protein on the target cell or a ligand for a receptor on the target cell can be bound to or  
20 incorporated within the nucleic acid delivery vehicle. Preferred antibodies include antibodies which selectively bind a cancer associated antigen, alone or as a complex with a MHC molecule.

Especially preferred are monoclonal antibodies. Where liposomes are employed to deliver the nucleic acids of the invention, proteins which bind to a surface membrane protein associated with endocytosis may be incorporated into the liposome formulation for targeting and/or to facilitate  
25 uptake. Such proteins include capsid proteins or fragments thereof tropic for a particular cell type, antibodies for proteins which undergo internalization in cycling, proteins that target intracellular localization and enhance intracellular half life, and the like. Polymeric delivery systems also have been used successfully to deliver nucleic acids into cells, as is known by those skilled in the art. Such systems even permit oral delivery of nucleic acids.

30 When administered, the therapeutic compositions of the present invention can be

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administered in pharmaceutically acceptable preparations. Such preparations may routinely contain pharmaceutically acceptable concentrations of salt, buffering agents, preservatives, compatible carriers, supplementary immune potentiating agents such as adjuvants and cytokines and optionally other therapeutic agents.

5           The therapeutics of the invention can be administered by any conventional route, including injection or by gradual infusion over time. The administration may, for example, be oral, intravenous, intraperitoneal, intramuscular, intracavity, subcutaneous, or transdermal. When antibodies are used therapeutically, a preferred route of administration is by pulmonary aerosol. Techniques for preparing aerosol delivery systems containing antibodies are well known to those of  
10 skill in the art. Generally, such systems should utilize components which will not significantly impair the biological properties of the antibodies, such as the paratope binding capacity (see, for example, Sciarra and Cutie, "Aerosols," in Remington's Pharmaceutical Sciences, 18th edition, 1990, pp 1694-1712; incorporated by reference). Those of skill in the art can readily determine the various parameters and conditions for producing antibody aerosols without resort to undue  
15 experimentation. When using antisense preparations of the invention, slow intravenous administration is preferred.

          The compositions of the invention are administered in effective amounts. An "effective amount" is that amount of a cancer associated antigen composition that alone, or together with further doses, produces the desired response, e.g. increases an immune response to the cancer  
20 associated antigen. In the case of treating a particular disease or condition characterized by expression of one or more cancer associated antigens, such as cancer, the desired response is inhibiting the progression of the disease. This may involve only slowing the progression of the disease temporarily, although more preferably, it involves halting the progression of the disease permanently. This can be monitored by routine methods or can be monitored according to  
25 diagnostic methods of the invention discussed herein. The desired response to treatment of the disease or condition also can be delaying the onset or even preventing the onset of the disease or condition.

          Such amounts will depend, of course, on the particular condition being treated, the severity of the condition, the individual patient parameters including age, physical condition, size and  
30 weight, the duration of the treatment, the nature of concurrent therapy (if any), the specific route of



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administration and like factors within the knowledge and expertise of the health practitioner. These factors are well known to those of ordinary skill in the art and can be addressed with no more than routine experimentation. It is generally preferred that a maximum dose of the individual components or combinations thereof be used, that is, the highest safe dose according to sound  
5 medical judgment. It will be understood by those of ordinary skill in the art, however, that a patient may insist upon a lower dose or tolerable dose for medical reasons, psychological reasons or for virtually any other reasons.

The pharmaceutical compositions used in the foregoing methods preferably are sterile and contain an effective amount of breast cancer associated antigen or nucleic acid encoding cancer  
10 associated antigen for producing the desired response in a unit of weight or volume suitable for administration to a patient. The response can, for example, be measured by determining the immune response following administration of the cancer associated antigen composition via a reporter system as described herein, by measuring downstream effects such as gene expression, or by measuring the physiological effects of the breast cancer associated antigen composition, such as  
15 regression of a tumor or decrease of disease symptoms. Other assays will be known to one of ordinary skill in the art and can be employed for measuring the level of the response.

The doses of cancer associated antigen compositions (e.g., polypeptide, peptide, antibody, cell or nucleic acid) administered to a subject can be chosen in accordance with different parameters, in particular in accordance with the mode of administration used and the state of the subject. Other  
20 factors include the desired period of treatment. In the event that a response in a subject is insufficient at the initial doses applied, higher doses (or effectively higher doses by a different, more localized delivery route) may be employed to the extent that patient tolerance permits.

In general, for treatments for eliciting or increasing an immune response, doses of cancer associated antigen are formulated and administered in doses between 1 ng and 1 mg, and preferably  
25 between 10 ng and 100  $\mu$ g, according to any standard procedure in the art. Where nucleic acids encoding cancer associated antigen or variants thereof are employed, doses of between 1 ng and 0.1 mg generally will be formulated and administered according to standard procedures. Other protocols for the administration of cancer associated antigen compositions will be known to one of ordinary skill in the art, in which the dose amount, schedule of injections, sites of injections, mode of  
30 administration (e.g., intra-tumoral) and the like vary from the foregoing. Administration of cancer

associated antigen compositions to mammals other than humans, e.g. for testing purposes or veterinary therapeutic purposes, is carried out under substantially the same conditions as described above.

As part of the immunization compositions, the peptide antigens are administered with one or more adjuvants to induce an immune response or to increase an immune response. An adjuvant is a substance incorporated into or administered with antigen which potentiates the immune response. Adjuvants may enhance the immunological response by providing a reservoir of antigen (extracellularly or within macrophages), activating macrophages and stimulating specific sets of lymphocytes. Adjuvants of many kinds are well known in the art. Specific examples of adjuvants include monophosphoryl lipid A (MPL, SmithKline Beecham), a congener obtained after purification and acid hydrolysis of *Salmonella minnesota* Re 595 lipopolysaccharide; saponins including QS21 (SmithKline Beecham), a pure QA-21 saponin purified from *Quillja saponaria* extract; DQS21, described in PCT application WO96/33739 (SmithKline Beecham); QS-7, QS-17, QS-18, and QS-L1 (So et al., *Mol. Cells* 7:178-186, 1997); incomplete Freund's adjuvant; complete Freund's adjuvant; montanide; and various water-in-oil emulsions prepared from biodegradable oils such as squalene and/or tocopherol. Other adjuvants are known in the art and can be used in the invention (see, e.g. Goding, *Monoclonal Antibodies: Principles and Practice*, 2nd Ed., 1986). Methods for the preparation of mixtures or emulsions of peptide and adjuvant are well known to those of skill in the art of vaccination.

Where cancer associated antigen peptides are used for vaccination, modes of administration which effectively deliver the cancer associated antigen and adjuvant, such that an immune response to the antigen is increased, can be used. For administration of a cancer associated antigen peptide in adjuvant, preferred methods include intradermal, intravenous, intramuscular and subcutaneous administration. Although these are preferred embodiments, the invention is not limited by the particular modes of administration disclosed herein. Standard references in the art (e.g., *Remington's Pharmaceutical Sciences*, 18th edition, 1990) provide modes of administration and formulations for delivery of immunogens with adjuvant or in a non-adjuvant carrier.

When administered, the pharmaceutical preparations of the invention are applied in pharmaceutically-acceptable amounts and in pharmaceutically-acceptable compositions. The term "pharmaceutically acceptable" means a non-toxic material that does not interfere with the

effectiveness of the biological activity of the active ingredients. Such preparations may routinely contain salts, buffering agents, preservatives, compatible carriers, and optionally other therapeutic agents. When used in medicine, the salts should be pharmaceutically acceptable, but non-pharmaceutically acceptable salts may conveniently be used to prepare pharmaceutically-acceptable salts thereof and are not excluded from the scope of the invention. Such pharmacologically and pharmaceutically-acceptable salts include, but are not limited to, those prepared from the following acids: hydrochloric, hydrobromic, sulfuric, nitric, phosphoric, maleic, acetic, salicylic, citric, formic, malonic, succinic, and the like. Also, pharmaceutically-acceptable salts can be prepared as alkaline metal or alkaline earth salts, such as sodium, potassium or calcium salts.

A breast cancer associated antigen composition may be combined, if desired, with a pharmaceutically-acceptable carrier. The term "pharmaceutically-acceptable carrier" as used herein means one or more compatible solid or liquid fillers, diluents or encapsulating substances which are suitable for administration into a human. The term "carrier" denotes an organic or inorganic ingredient, natural or synthetic, with which the active ingredient is combined to facilitate the application. The components of the pharmaceutical compositions also are capable of being co-mingled with the molecules of the present invention, and with each other, in a manner such that there is no interaction which would substantially impair the desired pharmaceutical efficacy.

The pharmaceutical compositions may contain suitable buffering agents, including: acetic acid in a salt; citric acid in a salt; boric acid in a salt; and phosphoric acid in a salt.

The pharmaceutical compositions also may contain, optionally, suitable preservatives, such as: benzalkonium chloride; chlorobutanol; parabens and thimerosal.

The pharmaceutical compositions may conveniently be presented in unit dosage form and may be prepared by any of the methods well-known in the art of pharmacy. All methods include the step of bringing the active agent into association with a carrier which constitutes one or more accessory ingredients. In general, the compositions are prepared by uniformly and intimately bringing the active compound into association with a liquid carrier, a finely divided solid carrier, or both, and then, if necessary, shaping the product.

Compositions suitable for oral administration may be presented as discrete units, such as

capsules, tablets, lozenges, each containing a predetermined amount of the active compound. Other compositions include suspensions in aqueous liquids or non-aqueous liquids such as a syrup, elixir or an emulsion.

Compositions suitable for parenteral administration conveniently comprise a sterile aqueous or non-aqueous preparation of breast cancer associated antigen polypeptides or nucleic acids, which is preferably isotonic with the blood of the recipient. This preparation may be formulated according to known methods using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation also may be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example, as a solution in 1,3-butane diol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or di-glycerides. In addition, fatty acids such as oleic acid may be used in the preparation of injectables. Carrier formulation suitable for oral, subcutaneous, intravenous, intramuscular, etc. administrations can be found in *Remington's Pharmaceutical Sciences*, Mack Publishing Co., Easton, PA.

### Examples

#### **Example 1: Preparation of breast cancer cDNA expression libraries**

Step 1: Purification of total RNA from tumors.

Total RNA was isolated from tumor samples using the guanidium thiocyanate-phenol-chloroform extraction protocol described by Chomczynski and Sacci (*Anal. Biochem.* 162:156-159, 1987).

Step 2: Purification of mRNA.

A Dynabeads mRNA isolation kit (Dynal, Cat.No. 610.01) was used to isolate mRNA from the pool of total RNA isolated in step 1 above according to the manufacturer's instructions.

Step 3: cDNA synthesis.

cDNA synthesis was performed using a ZAP-cDNA synthesis Kit (Stratagene, La Jolla CA; Cat. No. 200400) according to the manufacturer's protocol. A specific linker-primer which contains

a XbaI cloning site was designed and used in this protocol, to facilitate subcloning into TriplEx

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vector. The sequence of the primer was:

GAGAGAGAGAGAGAGAGAGAAGTCGACTCTAGATTTTTTTTTTTTTTTTTT-Xba I site

Step 4: Ligation into the TriplEx vector arms.

5 The cDNAs generated in step 3 above were ligated into TriplEx vector arms (Clontech, Palo Alto, CA; Cat. No. 6162-1); the arms were predigested with EcoR I/Xba I.

Step 5: Packaging into phages with Gigapack III kit.

The ligation mix (TriplEx/cDNA) from step 4 was packed into phages using the Gigapack III Gold Cloning Kit (Stratagene, Cat. N.200450) according to the protocol supplied with the kit.

10 Step 6: Titering and amplification of generated libraries was performed according to the Stratagene protocols.

The foregoing protocol was used to prepare several libraries from tumor sample of different patients. Some libraries were prepared using the UNI-ZAP XR vector system (Stratagene)  
15 according to the manufacturer's protocol, and some using the TriplEx system as described above.

Table 2

UNI-ZAP Libraries		
Code for tumors	Titer of the library	Histopathological diagnosis
20 HBR173	$1.8 \times 10^6$ pfu	Ductal Carcinoma, Grade III
HBR184	$3.5 \times 10^6$ pfu	Invasive Ductal Carcinoma, Grade II
TriplEx libraries		
Code for tumors	Titer of the library	Histopathological diagnosis
25 HBR173	$2.3 \times 10^6$ pfu	Ductal Carcinoma, Grade III
HBR184	$1.1 \times 10^6$ pfu	Invasive Ductal Carcinoma, Grade II
HBR257	$2.5 \times 10^6$ pfu	Invasive Ductal Carcinoma, Grade II
HBR297	$4.0 \times 10^6$ pfu	Ductal Carcinoma, Grade II
HBR248	$1.0 \times 10^6$ pfu	Invasive Ductal Carcinoma with Vascular Permeation, Grade III

HBR271	$2.5 \times 10^6$ pfu	Medullary Carcinoma
HBR263	$10.0 \times 10^6$ pfu	Inv. Pleiomorphic Lobular Carcinoma, Grade II

All libraries were screened with the exception of HBR173 (no autologous serum). No  
5 serum-positive clones were found by screening HBR271 library.

### Example 2: Immunoscreening

Sera was obtained from donors undergoing routine diagnostic and therapeutic procedures. It was stored at  $-70^{\circ}\text{C}$  prior to absorption. Sera, at a dilution of 1:10 in Tris buffered saline (TBS, pH  
10 7.5), was sequentially passed through Sepharose 4B columns which had been coupled to lysates from *E. coli* Y1090 and bacteriophage infected *E. coli* BNN97 (5 Prime 3 Prime, Inc. Boulder, Co.). Final serum dilutions were prepared in 0.2% non-fat dried milk/TBS (NFDM) and stored at  $4^{\circ}\text{C}$ . Library screening was performed as described by Sahin et al. (*Proc. Natl. Acad. Sci. USA* 92:11810-11813, 1995) with following modifications. Recombinant phage at a concentration of  $4 \times$   
15  $10^3$  per 15 cm plate were amplified for 6 hours and transferred to nitrocellulose membranes for an additional 15 hours at  $37^{\circ}\text{C}$ . Membranes were then blocked with 5% NFDM. As an alternative to generation of IgG subtracted libraries, membranes were pre-screened in a 1:2000 dilution of peroxidase conjugated, Fc fragment specific, goat anti-human IgG (Jackson ImmunoResearch Laboratories Inc., West Grove, PA) for 1 hour at room temperature. Color was developed with 3,3'  
20 diaminobenzidine tetrahydrochloride and IgG encoding clones were scored. Membranes were then incubated in a 1:100 dilution of absorbed autologous sera for 15 hours at room temperature. Following serum exposure, filters were incubated in a 1:3000 dilution of alkaline phosphatase conjugated, Fc fragment specific, goat anti-human IgG (Jackson ImmunoResearch Laboratories Inc.) for 1 hour at room temperature and processed for 4-nitro blue tetrazolium  
25 chloride/5-bromo-4-chloro-3-indolyl-phosphate color development. Serum positive clones were subcloned and retested for serum reactivity as above except nitrocellulose transfer was decreased to 3 hours. For the determination of allogeneic serum reactivity, plates containing an equal number of serum positive clones and negative control plaques were similarly processed less the IgG prescreening steps. A minimum of  $5 \times 10^5$  recombinants were screened per cDNA library, a number

which approximates a point at which the likelihood of repeat isolations of previously identified clones outweigh the prospect of identifying new clones.

### Example 3: DNA Sequencing

5        Phage cDNA clones were converted to pBKCMV phagemid forms by in vivo excision. Plasmid DNA was purified on Qiaprep spin columns (Qiagen Inc. Chatsworth, CA) and subjected to EcoRI/XbaI restriction enzyme digestion. Clones representing different cDNA inserts were sequenced at Cornell University DNA services (Ithaca, NY) using an ABI Prism (Perkin Elmer) automated DNA sequencer. The sequences of the clones were compared with sequences in  
10    GenBank and HGI databases to detect homologous nucleic acid and/or protein sequences. The following table lists exemplary related sequences.

Table 3: Sequences Related to Breast Cancer Associated Antigen Clones

Clone	Nucleotide Homology	Clone	Nucleotide Homology	Clone	Nucleotide Homology
15 LONY-Br-1	L34543	LONY-Br-23	AA262134, U74628	LONY-Br-44	D15057
LONY-Br-2	S75417	LONY-Br-24	AA282633	LONY-Br-45	AB000815
LONY-Br-3	J05211	LONY-Br-25	M62324	LONY-Br-46	L04733
LONY-Br-4	X15187	LONY-Br-26	M99389	LONY-Br-47	X88791
LONY-Br-5	X62083	LONY-Br-27	X79389	LONY-Br-48	AF000430
20 LONY-Br-6	J04965	LONY-Br-28	D44466	LONY-Br-49	none
LONY-Br-7	D63784	LONY-Br-29	M33197	LONY-Br-50	AA226732
LONY-Br-8	U11292	LONY-Br-30	M17886	LONY-Br-51	AA046574
LONY-Br-9	HSB06D102	LONY-Br-31	L38941	LONY-Br-52	none
LONY-Br-10	none	LONY-Br-32	X17644	LONY-Br-53	AB002307
25 LONY-Br-11	none	LONY-Br-33	X75342	92	AA127328
LONY-Br-12	AA430998	LONY-Br-33	X75342	101	AA167314
LONY-Br-13	D83032	LONY-Br-34	U43368	102	AA508139
LONY-Br-14	AA034417	LONY-Br-35	X15882	107	none
LONY-Br-15	AA167070	LONY-Br-37	AA121558	109	AA220229

LONY-Br-16	none	LONY-Br-38	AA211771	110	W67775
LONY-Br-17	AA161103	LONY-Br-39	AA367417	111	AA280070
LONY-Br-19	R13835	LONY-Br-40	AA188052	112	AF004292
LONY-Br-20	HUMORF003	LONY-Br-41	THC83518	131	none
LONY-Br-21	S74572	LONY-Br-42	none	143	AA481578
LONY-Br-22	AA070233	LONY-Br-43	HU35246	162	AA481578

#### Example 4: Reverse transcriptase (RT) PCR and Rapid Amplification of cDNA Ends (RACE)

The mRNA expression pattern of selected cDNA clones was determined by RT-PCR using a panel of normal tissue RNA. This test panel consisted of lung, testis, small intestine, colon, breast, liver, and placenta, and was purchased from Clontech Laboratories Inc. (Palo Alto, CA). Colon tumor RNA was also included in this panel and was prepared as described above. As a control for genomic DNA contamination, all cDNA synthesis reactions were set up in duplicate with the additional sample lacking reverse transcriptase. Gene specific PCR primers were designed to amplify 5' fragments of 300-400 bp and were purchased commercially (Gibco BRL, Grand Island, NY). PCR reactions were undertaken at an annealing temperature of 68°C using a Perkin Elmer thermal cycler. In certain cases, RT-PCR products were subcloned into the pCR2.1 plasmid vector (Invitrogen) and multiple clones were subjected to DNA sequencing as described. 5' and 3' RACE reactions were undertaken using gene specific and adapter primers in conjunction with Marathon Ready normal colon cDNA and KlenTaq polymerase (Clontech) as per manufacturers protocol. Products were then subcloned into the pCR2.1 plasmid vector (Invitrogen) and screened by PCR with internal primers for presence of the desired insert. Multiple RACE clones were subjected to DNA sequencing as described.

#### Example 5: Northern blot analysis

Northern blots containing the transfer yields of 2 µg poly A<sup>+</sup> RNA from a panel of normal tissues were obtained commercially (Clontech). Random primed <sup>32</sup>P labeled probes consisting of 300-600 bp PCR products from 5 prime coding sequences of serum positive cDNA clones were hybridized for 1.5 hours in Expresshyb (Clontech) at 68°C and washed at high stringency (2 times,



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30 min. each, 0.1X SSC/0.1% SDS at 68°C). Resultant blots were used to expose Biomax MS autoradiography film (Eastman Kodak Co., Rochester, NY).

Table 4: Breast Cancer Associated Antigen Clone mRNA sizes

5	Clone	Size (kb)	Clone	Size (kb)	Clone	Size (kb)
	LONY-Br-1	1.8	LONY-Br-17	1.0	LONY-Br-33	2.6
	LONY-Br-2	2.9	LONY-Br-19	1.5	LONY-Br-34	2.1
	LONY-Br-3	4.8	LONY-Br-20	2.4	LONY-Br-35	1.9
	LONY-Br-4	1.2	LONY-Br-21	2.4	LONY-Br-36	0.8
10	LONY-Br-5	0.9	LONY-Br-22	1.6	LONY-Br-37	1.0
	LONY-Br-6	1.4	LONY-Br-23	1.3	LONY-Br-38	2.2
	LONY-Br-7	1.3	LONY-Br-24	3.9	LONY-Br-39	1.9
	LONY-Br-8	0.9	LONY-Br-25	1.9	LONY-Br-40	3.4
	LONY-Br-9	6.0	LONY-Br-26	1.5	LONY-Br-41	3.9
15	LONY-Br-10	3.6	LONY-Br-27	1.2	LONY-Br-42	0.6
	LONY-Br-11	4.6	LONY-Br-28	0.5	LONY-Br-43	1.4
	LONY-Br-12	2.2	LONY-Br-29	0.6	LONY-Br-44	0.7
	LONY-Br-13	1.2	LONY-Br-30	0.8	LONY-Br-45	3.0
	LONY-Br-14	0.8	LONY-Br-31	0.4	LONY-Br-46	3.7
20	LONY-Br-15	0.9	LONY-Br-32	2.2	LONY-Br-47	0.5
	LONY-Br-16	2.5	LONY-Br-33	2.6	LONY-Br-48	1.6

#### **Example 6: Isolation of gastric and prostate clones**

A stomach cancer cDNA library was established, using standard techniques, then the library  
 25 was screened, using the SEREX methodology described supra, and set forth by Sahin et al., *Proc. Natl. Acad. Sci. USA* 92: 11810 (1995), and by Chen et al., *Proc. Natl. Acad. Sci. USA* 94: 1914 (1997), incorporated by reference in their entirety.

To be specific, total RNA was isolated by homogenizing tumor samples in 4M guanidium thiocyanate/0.5% sodium N-lauryl sarcosine/ and 25 mM EDTA followed by centrifugation in 5.7  
 30 M CsCl/25 mM sodium acetate/10 uM EDTA at 320,000 rpm. Total mRNA was removed by passing the sample over an oligo-dT cellulose column. The cDNA libraries were then constructed

by taking 5 ug of mRNA, using standard methodologies to reverse transcribe the material.

Libraries were prepared from four different stomach cancer patients, referred to as "SM", "CK" and "SS" and "KM" respectively. A total of  $2.5 \times 10^6$ ,  $1.1 \times 10^6$ , and  $1.7 \times 10^6$  cDNA clones were obtained from the "SM", "CK" and "SS" individuals. Additional libraries were prepared from prostate cancer patient "OT".

The cDNA was used to construct a lambda phage library, and 500 phages were plated onto XL1-Blue MRF E. coli, and incubated for eight hours at 37°C. A nitrocellulose membrane was then placed on the plate, followed by overnight incubation. The membrane was then washed, four times, without TBS which contained 0.05% Tween, and was then immersed in TBS containing 5% non-fat dried milk. After one hour, the membrane was incubated with conjugates of peroxidase-goat anti human IgG specific for Fc portions of human antibody (1:2000, diluted in TBS with 1% BSA. The incubation was carried out for one hour, at room temperature, and the membrane was then washed three times with TBS. Those clones which produced antibodies were visualized with 0.06%, 3,3'-diamino benzidine tetrachloride, and 0.015%  $H_2O_2$ , in 50 mM Tris (pH 7.5). Any clones which produced immunoglobulin were marked, and then the membrane was washed, two further times, with TBS that contained 0.05% Tween, and then twice with "neat" TBS.

The membranes were then incubated in 1:100 diluted patient serum, overnight, at 4°C. The patient serum had been pretreated. Specifically, 5 ml samples were diluted to 10 ml with TBS containing 1% bovine serum albumin, and 0.02%  $Na_3N$ . The serum had been treated to remove antibodies to bacteriophage, by passing it through a 5 ml Sepharose column, to which a lysate of E. coli Y1090 had been attached, followed by passage over a second column which had E. coli lysate and lysate of E. coli infected with lambda bacteriophage. The screening was carried out five times. The samples were then diluted to 50 ml, and kept at -80°C, until used as described herein.

Following the overnight incubation with the membrane, the membrane was washed twice with TBS/0.05% Tween 20, and then once with TBS. A further incubation was carried out, using the protocols discussed supra, for the POD labelled antibodies.

The positive clones were then sequenced, using standard techniques. Following comparison of the sequences to information available in data banks, a total of 36 clones were resolved into known and unknown genes. In the table that follows, the "+" and "-" signs are essentially used to compare signals to each other. All were positive. Table 5, which follows, summarizes some of this

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work isolation and sequencing of "SM" clones. Specifically, with reference to the first page of the table, previously identified human proteins and the nucleotide sequences, set forth in SEQ ID NOS:588-626 are known. The four molecules which follow in SEQ ID NOS:627-634 (gelsolin, zinc finger protein family, variant zinc finger motif protein goliath and homeodomain proteins), have not  
5 been identified in humans previously, although there are related molecules found in other species. Finally, with reference to Table 5, the last four moieties, i.e., prepro- $\alpha$  collagen, heterogeneous ribonucleoprotein D, nucleosome assembly protein 2, and NY-ESO-2/Ulsn NRP/V1 small nuclear ribonucleoprotein, are also known. Nucleotide sequences are set forth at SEQ ID NOS:635-642. The nucleic acid molecules having the nucleotide sequences set forth at SEQ ID NOS:643-670  
10 represent molecules for which no related sequences were found. SEQ ID NO:671 combines the sequences of SEQ ID NOS:627-630, inclusive. SEQ ID NO:672 combines SEQ ID NOS:643-656, SEQ ID NO:673 combines SEQ ID NOS:657, 659 and 662, while SEQ ID NO:674 combines SEQ ID NOS: 658, 660, 661 and 663.

SEREX analysis of clones from libraries derived from patients "CK", "SS", "KM" (all  
15 gastric cancer) and patient "OT" (prostate cancer) was carried out as described above. The nucleotide sequences of clones derived from gastric cancer patients are presented as SEQ ID NOS:176-436. The nucleotide sequences of clones derived from prostate cancer patient "OT" are presented as SEQ ID Nos:437-543.

#### 20 **Example 7: Isolation and analysis of colon clones**

Colon tumor samples were obtained as surgical samples, and were frozen at -80°C until ready for use.

Total RNA was then isolated from the samples, using the guanidium thiocyanate method of Chirgwin, et al., *Biochemistry* 18: 5294-5299 (1979), incorporated by reference. The total RNA thus  
25 obtained was then purified to isolate all poly A<sup>+</sup> RNA, using commercially available products designed for this purpose.

The poly A<sup>+</sup> RNA was then converted into cDNA, and ligated into  $\lambda$ ZAP, a commercially available expression vector, according to the manufacturer's suggested protocol.

Three cDNA libraries were constructed in this way, using colorectal carcinoma samples.

30 A fourth library, also from colorectal carcinoma, was prepared, albeit in a different way. The

fourth library was an IgG subtraction library, prepared by using a subtraction partner, generated by PCR amplification of a cDNA clone which encoded an IgG molecule. *See, e.g., Ace et al, Endocrinology* 134: 1305-1309 (1994), and incorporated by reference in its entirety. IgG subtraction is done to eliminate any false, positive signals resulting from interaction of cDNA clones which encode IgG, with the IgG then interacting with the anti-human IgG used in the SEREX assay, as described herein. PCR products were biotinylated, and hybridized with denatured second strand cDNA, at 68°C for 18 hours. Biotinylated hybrid molecules were coupled to streptavidin, and then removed by phenol chloroform extraction. Any remaining cDNA was also ligated into  $\lambda$ ZAP. All libraries were amplified, prior to immunoscreening.

Immunoscreening was carried out using sera obtained from patients undergoing routine diagnostic and therapeutic procedures. The sera were stored at -70°C prior to use. Upon thawing, the sera were diluted at 1:10 in Tris buffered saline (pH 7.5), and were then passed through Sepharose 4B columns. First, the sera were passed through columns which had *E. coli* Y1090 lysates coupled thereto, and then lysates from bacteriophage infected *E. coli* BNN97 lysates. Final serum dilutions were then prepared in 0.2% non-fat dried milk/Tris buffered saline.

The method of Sahin et al., *Proc. Natl. Acad. Sci. USA* 92:11810-11813 (1995), and U.S. Patent No. 5,698,396, both of which are incorporated by reference, was used, with some modifications. Specifically, recombinant phages at a concentration of  $4 \times 10^3$  phages per 15 cm plate (pfus), were amplified for six hours, after which they were transferred to nitrocellulose membranes for 15 hours. The membranes then were blocked with 5% nonfat dried milk.

As an alternative to the IgG subtraction procedure discussed above, membranes were prescreened in a 1:2000 dilution of peroxidase conjugated, Fc fragment specific goat anti-human IgG, for one hour, at room temperature. Color was developed using 3,3'-diaminobenzidine tetrahydrochloride, which permitted scoring of IgG encoding clones.

Membranes were then incubated in 1:100 dilutions of autologous sera, which had been pretreated with the Sepharose 4B columns, as described *supra*. The filters were then incubated, in a 1:3000 dilution of alkaline phosphatase conjugated Fc fragment specific, goat anti-human IgG, for one hour, at room temperature. The indicator system 4-nitroblue tetrazolium chloride/5-bromo-4-chloro-3-indolyl-phosphate was then added, and color development assessed. Any positive clones were subcloned, and retested, except the time on the nitrocellulose membrane was reduced to three

hours.

Positive clones were isolated and sequenced according to standard procedures. The nucleotide sequences of the clones are set forth in the even numbered sequences from SEQ ID Nos:544-586. The odd numbered sequences from SEQ ID Nos:545-587 represent the translated amino acid sequences of the colon nucleic acid clones. Analysis of probes for SEQ ID NOS:544 and 546 confirmed their universal expression.

The foregoing results reflect SEREX isolation of colon cancer clones using autologous serum. The positive clones were then rescreened, using allogeneic serum, following the same method discussed supra, in example 2, except IgG prescreening was omitted. The allogeneic sera was obtained from sixteen normal blood donors, and twenty nine patients who had been diagnosed with colorectal cancer.

The analysis with the two types of serum revealed that fourteen reacted with a subset of sera from normal and cancer patients, twenty-eight only with autologous sera, and six with both allogeneic and autologous sera. Over 60% of the allogeneic serum samples tested reacted with at least one of these positive clones. About 20% reacted with two or more.

In view of the results described above, further experiments were carried out using serum samples from patients with other forms of cancer, i.e., renal cancer (13 samples), lung cancer (23 samples), and breast cancer (10 samples). The results are set forth in Table 6 which follows:

Table 6: Allogeneic serotyping using colon cancer clones

Clone Number	Normal Sera	Colon Cancer	Renal Cancer	Lung Cancer	Breast Cancer
NY-Co-8	0/16	8/29	1/13	0/23	0/10
NY-Co-9	0/16	5/29	1/13	1/23	0/10
NY-Co-13	0/16	5/29	0/13	0/23	0/10
NY-Co-16	0/16	3/29	0/13	0/23	0/10
NY-Co-20	0/16	4/29	0/13	0/23	0/10
NY-Co-38	0/16	4/29	3/13	0/23	1/10

Of the six clones which were identified as being reactive with autologous and allogeneic

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cancer serum, and not with normal serum, two were found to be identical to previously identified molecules (NY-Co-. Four others were found to have little or no homology to known sequences and thus are preferred allogeneic-reactive colon cancer clones. These nucleic acids and their polypeptide translations are presented as SEQ ID NOS: 544-551: SEQ ID NO: 544/545 (NY-CO-8), SEQ ID NO: 546/547 (NY-CO-9), SEQ ID NO: 548/549 (NY-CO-16) and SEQ ID NO: 550/551 (NY-CO-38). . Of twenty seven allogeneic colon cancer serum samples tested, 67% reacted with at least one of these antigens.

The expression pattern of mRNA corresponding to SEQ ID NOS:544, 546 and 550, as well as other sequences identified via the preceding examples was determined. To do this, RT-PCR was carried out on a panel of RNA samples, taken from normal tissue. The panel contained RNA of lung, testis, small intestine, colon, breast, liver and placenta tissues. The RNA was purchased from a commercial source. RNA from a colon tumor sample was also included. All samples were set up for duplicate runs, so that genomic DNA contamination could be accounted for. In the controls, no reverse transcriptase was used.

Primers were designed which were specific for the cDNA, which would amplify 5'-fragments, from 300-400 base pairs in length. The PCR reactions were undertaken at an annealing temperature of 68°C. Where appropriate, 5' and 3'-RACE reactions were undertaken, using gene specific primers, and adapter primers, together with commercially available reagents. Specifically, SEQ ID NOS: 546 and 550 were tested using RACE. The resulting products were subcloned into vector pCR 2.1, screened via PCR using internal primers, and then sequenced.

SEQ ID NOS:544 and 546 were found to be amplified in all tissues tested. SEQ ID NO:550 was found in colon tumor, colon metastasis, gastric cancer, renal cancer and colon cancer cell lines Colo 204 and HT29, as well as in normal colon, small intestine, brain, stomach, testis, pancreas, liver, lung, heart, fetal brain, mammary gland, bladder, adrenal gland tissues. It is was not found in normal uterine, skeletal muscle, peripheral blood lymphocytes, placental, spleen thymus, or esophagus tissue, nor in lung cancer.

The analysis also identified differential expression of a splice variant of SEQ ID NO:550, i.e., SEQ ID NO:552. When the two sequences were compared, it was found that SEQ ID NO:550 encodes a putative protein of 652 amino acids (SEQ ID NO:551), and molecular weight of 73,337 daltons. SEQ ID NO:552, in contrast, lacks an internal 74 base pairs, corresponding to

nucleotides 1307-1380 of SEQ ID NO:550. The deletion results in formation of a stop codon at the splice function, and a putative protein of 403 amino acids (SEQ ID NO:553), and molecular weight 45,839. The missing segment results in the putative protein lacking a PEST protein degradation sequence, thereby suggesting a longer half life for this protein.

5 In additional experiments, primers designed not to differentiate between SEQ ID NOS: 550 and 552 resulted in almost universal amplification (placenta being the only exception). In contrast, when primers specific for SEQ ID NO:552 were used differences were seen in normal pancreatic, liver, lung, heart, fetal brain, mammary gland, bladder, and adrenal gland tissue, where there was no expression of SEQ ID NO:552 found.

10 Northern blotting was also carried out for SEQ ID NOS: 544, 546, 550 and 552. These experiments employed the same commercially available RNA libraries discussed above were used.

Samples (2 ug) of polyA<sup>+</sup> RNA were analyzed from these samples, using random, <sup>32</sup>P labelled probes 300-360 nucleotides in length, obtained from PCR products. These probes were hybridized to the RNA, for 1.5 hours, at 68°C, followed by two washes at 0.1xSSC, 0.1% SDS, 15 68°C, for 30 minutes each time.

SEQ ID NOS:544 and 546 were again found to be universally expressed.

Further screening identified additional isoforms of SEQ ID NOS:544 and 550. These are set forth as SEQ ID NOS: 554, 556, 558 and 560. The isoform represented by SEQ ID NO:554 (translated as SEQ ID NO:555) is a naturally occurring splice variant of SEQ ID NO:544, found 20 in normal colon. SEQ ID NO:556 (translated as SEQ ID NO:557), which is an isoform of SEQ ID NO:550 (translated as SEQ ID NO:551), was found in brain tissue, primarily spinal chord and medulla. SEQ ID NO:558 (translated as SEQ ID NO:559), was found in normal kidney and in colon tumors, metastasized colon cancer, renal cancer, gastric cancer, and in colon cancer cell line Colo 205. It was not found in any normal tissue other than kidney.

25 The nucleic acid molecule whose nucleotide sequence set forth as SEQ ID NO:560 (translated as SEQ ID NO:561), is a further isoform of SEQ ID NO:552. It is similar to SEQ ID NO:558, except it contains a long nucleotide insert encoding a longer COOH terminus. It was expressed in normal bladder and kidney cells, and renal cancer cells. It was not expressed in colon cancer cells.

30 It is reported above that fourteen clones reacted with subsets of serum from both normal

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and cancer patients, while twenty eight reacted with autologous sera only. These clones were sequenced, in accordance with standard, art recognized methods. Of the clones which reacted only with autologous sera, nine appear to be previously unidentified sequences. These are set forth as SEQ ID NOS: 562, 564, 566, 568, 570, 572, 574, 576 and 578. SEQ ID NO:562 (translated as SEQ ID NO:563) is 1445 nucleotides long, and shows some similarity to known sequences for myosin and tropomyosin. SEQ ID NO:564 (translated as SEQ ID NO:565), which is 1226 nucleotides long, contains a TPR motif. The sequence set forth in SEQ ID NO:566 (translated as SEQ ID NO:567) is 1857 nucleotides long, and shows similarity to cyclophilins. The nucleotide sequence set forth in SEQ ID NO:568 (translated as SEQ ID NO:569) is 1537 nucleotides long, and shows similarity to murine gene 22A3, which has unknown function, but resembles an unconventional form of myosin, as well as an EST for heat shock inducible mRNA. As for the molecule set forth in SEQ ID NO:570 (translated as SEQ ID NO:571), it appears to resemble a nucleic targeting signal protein. SEQ ID NO: 572 (translated as SEQ ID NO:573) is 604 nucleotides long, and may encode a lysosomal protein. The molecule set forth in SEQ ID NO:574 (translated as SEQ ID NO:575) is 742 nucleotides long, and encodes a protein with an SH3 domain and which shows some similarity to GRB2 and human neutrophil oxidase factor. The molecule set forth in SEQ ID NO:576 (translated as SEQ ID NO:577) is 1087 nucleotides long, and encodes a protein which contains coiled core domains. The molecule set forth in SEQ ID NO:578 (translated as SEQ ID NO:579) is 2569 nucleotides long, shows some similarity with *Drosophila* homeotic material tudor protein, and has a DY(F)GN repeat.

Additional sequences were identified which were expressed in both normal sera and cancer cells. The sequence set forth in SEQ ID NO:580 (translated as SEQ ID NO:581), e.g., is 2077 nucleotides long, and was expressed by both colorectal cancer and normal cells. Analysis of the sequence showed that it possesses a nuclear targeting sequence. The molecule set forth in SEQ ID NO:582 (translated as SEQ ID NO:583) is 3309 nucleotides long, was expressed by colorectal cancer and normal cells, and is similar to heat shock protein 110 family members. The molecule presented in SEQ ID NO:584 (translated as SEQ ID NO:585) was expressed in a colon to lung metastasis, as well as by normal tissue. It is 2918 nucleotides in length. Analysis shows that it contains 2 zinc finger domains. The nucleotide sequence of SEQ ID NO:586 (translated as SEQ ID NO:587) was also expressed in a colon to lung metastasis, is 1898 nucleotides long, and is



also expressed by normal tissue. Specifically, the reactivity of the molecules was as follows:

Table 7

	SEQ ID NO:	Normal Sera Reactivity	Tumor Sera Reactivity
5	580	2/16	2/16
	582	2/16	3/16
10	584	2/16	2/16
	586	2/8	1/16

A more extensive set of RT-PCR experiments were carried out to study the expression pattern of SEQ ID NOS: 550, 552, 558 and 560. The results follow.

15

Table 8: RT-PCR analysis of colon SEREX clones

	<u>normal tissue</u>	<u>SEQ ID NO.:550</u>	<u>SEQ ID NO.:552</u>	<u>SEQ ID NO.:558</u>	<u>SEQ ID NO.:560</u>
20	kidney	+	Negative	Negative	Negative
	colon	+	Negative	Negative	Negative
	small		Negative	Negative	Negative
	intest.	+	Negative	Negative	Negative
	brain	+	Negative	Negative	Negative
25	stomach	+	Negative	Negative	Negative
	testis	+	Negative	Negative	Negative
	pancreas	+	Negative	Negative	Negative
	lung	+	Negative	Negative	Negative
	liver	+	Negative	Negative	Negative
30	heart	+	Negative	Negative	Negative
	fetal		Negative	Negative	Negative
	brain	+	Negative	Negative	Negative
	mammary		Negative	Negative	Negative
	gland	+	Negative	Negative	Negative
35	bladder	+	Negative	Negative	Negative
	adrenal		Negative	Negative	Negative
	gland	+	Negative	Negative	Negative
	uterus	Negative	Negative	Negative	Negative
	skeletal		Negative	Negative	Negative
40	muscle	Negative	Negative	Negative	Negative
	PBL	Negative	Negative	Negative	Negative
	placenta	Negative	Negative	Negative	Negative

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	spleen	Negative	Negative	Negative	Negative
	thymus	Negative	Negative	Negative	Negative
	esophagus	Negative	Negative	Negative	Negative
	<u>Tumor Tissue</u>				
5	renal cancer (4)	+ (2/4)	+ (2/4)	+ (2/4)	+ (2/4)
	colon primary tumors (10)	+ (10/10)	+ (10/10)	+(10/10)	Negative
10	colon mets (4)	+ (4/4)	+ (4/4)	+ (4/4)	Negative
	breast cancer (6)	+ (3/6)	Negative	Negative	Negative
	lung cancer (6)	+ (6/6)	Negative	Negative	Negative
15	gastric cancer (1)	+	+	+	Not tested
	<u>colon cancer cell lines</u>				
	colo 205	+	+	+	Negative
	HT29	+	+	Negative	Negative
20	HCT15	Negative	Negative	Negative	Negative

**Example 8: Isolation and analysis of additional clones**

For the establishment of a cDNA library from human tissue total RNA was obtained from

25 0.5 g of a renal clear cell carcinoma and established according to the method of Chomzynski as described above. The mRNA was extracted from total RNA with oligo-dT-cellulose. The synthesis of the first strand cDNA was accomplished by the method described by Gubler and Hoffmann, *Gene* 25: 263 (1983) using RNase H and DNA polymerase I. For adaptation of the cDNA Klenow enzyme, adaptors with EcoRI restriction enzyme sites were ligated to the cDNA ends using T4 DNA

30 ligase (Ferretti L and Sgamerella V, *Nucl. Acids Res.* 9: 3695 (1981)). Following restriction enzymatic digestion with the enzyme XhoI, cDNA molecules of different length were separated using Sephacryl 400 and transfected into  $\lambda$ ZAPII phage vectors (Short JM et al., *Nucleic Acids Res.* 16: 7583 (1988)). The recombinant phage DNA was packaged into phages after ligation with packaging extracts and used for the transfection of *E. coli* bacteria. The titration of the library

35 resulted in  $1.8 \times 10^6$  recombinant primary clones. The total cDNA library was transfected in *E. coli* and amplified. The titer of the cDNA library after amplification was  $10^{11}$  plaque forming units per ml (pfu/ml). These transfected cells were used in experiments which follow.

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In accordance with the invention as described above, identification of immunogenic material was achieved by using human sera which has been completely depleted of antibodies directed against antigens derived from native and lytic  $\lambda$  phage-transfected *E. coli* bacteria. To this end, the serum was absorbed, as follows.

5        *E. coli* bacteria of the strain XL1-blue were cultured in 50 ml LB medium overnight. After achieving an optical density of  $OD_{600} = 1.0$ , the bacteria were pelleted by centrifugation, resuspended in 5 ml phosphate buffered saline (PBS), and lysed by sonication. The bacterial lysate was bound onto a matrix of activated Sepharose, which was then put into a column and used for the absorption of the human serum. The serum was run over this column 10 times.

10        A culture of *E. coli* XL1 blue bacteria in the exponential growth phase was pelleted by centrifugation, transfected in 0.01 M magnesium sulfate with  $10^6$   $\lambda$ ZAPII phages without a recombinant insert and incubated in 5 ml LB medium for four hours. The lysate of the transfected bacteria was used in the same manner as the untransfected bacteria, with the human serum described supra being passed through the column an addition ten times.

15        To complete the depletion of the serum, interfering antibodies from lytically transfected *E. coli* bacteria were cultured on agar plates and their proteins were blotted onto nitrocellulose membranes after 10 hours of culture at 37°C. Following this, the serum which had been preabsorbed according to the above steps was transferred to the blotted nitrocellulose membrane, and the absorption procedure was repeated five times. The serum, which was processed in  
20        accordance with the invention, was totally depleted of antibodies directed against antigens derived from *E. coli* and phages.

In this, a renal cancer-specific antigen was identified via the following steps. Bacteria of the strain XL1 blue were transfected with recombinant phages derived from the described cDNA library and plated at a density of  $4-5 \times 10^3$  plaque forming units (pfu) per plate in LB-medium with  
25        isopropylthiogalactopyranoside ("IPTG"). After 12 hours of incubation at 37°C, nitrocellulose membranes were put on top of the cultures and culture plates were incubated for another four hours. This was followed by incubation of the nitrocellulose membrane for one hour in Tris-buffered saline (PBS) with 5% milk powder. After washing the nitrocellulose membranes three times in TBS, the stripped human serum secured following Example 2 was diluted 1:1000 in TBS/0.5% (w/v) milk  
30        power and incubated overnight with gentle shaking. After the incubation with the nitrocellulose

membrane the serum was removed and kept for additional testing. Following incubation with serum, the nitrocellulose membranes were washed three times in TBS, and incubated with a polyclonal alkaline phosphatase-conjugated goat anti-human IgG serum for one hour. Following this, the nitrocellulose membranes were washed repeatedly with TBS/0.01% (v/v Tween 20). The reaction was developed using nitroblue tetrazolium chloride and bromochloro-indoyl-phosphate in TBS. The binding of human antibodies to the expressed protein became visible by a blue ring-formed color deposit on the nitro-cellulose membrane. The efficient preabsorption of the serum made it possible to develop the membrane at 37°C over several hours without compromising the quality of the test because of background reactivity caused by antibodies against *E. coli* and phage antigens.

Positive clones were localized on the agar plates, transferred into transfection buffer, and used for a second round of transfection and subcloning. A total of  $1.8 \times 10^6$  recombinant clones were subjected to screening and five different positive-reacting clones were identified.

Positive clones, i.e., those which had bound antibodies derived from the processed human serum, were subcloned to monoclonality by repeated rounds of transfection and testing of reactivity with the processed human serum. P-bluescript phagemids with the respective cDNA inserts were cloned by *in vivo* excision (Hay B and Short JM, *Strategies* 5: 16-19, 1992) from the  $\lambda$ ZAPII phage vectors and used for the transfection of *E. coli* SOLR bacteria. Plasmids were isolated from the bacteria after alkaline lysis with NaOH in a modification of the method of Birnboim HC and Doly J. *J. Nucl. Acids Res.* 7: 1513 (1979). The recombinant plasmid DNA was sequenced according to standard methods using M13-forward and M13-reverse oligonucleotides. The DNA sequence obtained and the resulting amino acid sequence were compared with nucleic acid and protein data banks (Gene Bank, EMBL, Swiss Prot). The sequencing of the cDNA inserts was continued using internal oligonucleotides. Analysis showed no homology with any sequences deposited in the data banks. The full length cDNA clone, referred to as SK313, was cloned with the RACE method (Frohman MA, Dush MK, Martin GR, *Proc. Natl. Acad. Sci. USA* 85: 8998 (1988)), and had a carbonic anhydrase domain at the 5' end.

As a continuation of these experiments, RNA was isolated from a spectrum of malignant and normal human tissues and Northern blots were performed with labeled SK313 (also referred to as clone HOM-RCC-313). The Northern blot analysis demonstrated that the mRNA of clone HOM-

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RCC-313 was overexpressed in 4 out of 19 renal cell carcinomas compared to normal kidneys. Very weak expression was found only in colonic mucosal tissue and in normal kidney. Expression in other tissues was not observed.

To determine the incidence of antibodies against antigens which are identified above,  
5 allogeneic sera from healthy individuals and tumor patients were analyzed. To this end, the sera were processed as described above and depleted from antibodies against antigens derived from *E. coli* and phages. For the detection of antigen-specific antibodies, phages derived from reactive clones were mixed with non-reactive phages derived from the same cDNA library at a ratio of 1:10 and tested as described above for reactivity with antibodies in the human test serum. The serum  
10 which had been used for the identification of the antigen was used as a positive control. The non-reactive phages served as a negative control. A serum sample was positive for antigen reactive antibodies, if the expected percentage of the phage plaques showed a positive reaction. In the case of the renal cell carcinoma antigen represented by clone HOM-RCC-313, the analysis of a spectrum of human sera showed that only sera from renal cell carcinoma patients contained reactive  
15 antibodies. Sera from healthy controls and patients with other tumors did not contain such antibodies.

The cDNA for clone HOM-RCC-313 was excised from the plasmid DNA by digestion with the restriction enzyme EcoR1, was separated by agarose gel electrophoresis, followed by extraction from the gel. This was then used to create a vector which expresses a fusion protein with the  
20 bacterial protein anthranilate synthetase. A relevant fragment in the exact open reading frame was cloned into pATH plasmid vectors (Koerner et al., *Meth. Enzymol.* 194: 477 (1991)). Induction of protein expression was obtained after transformation of the plasmids into *E. coli* of strain BL21 as described (Spindler et al., *J. Virol.* 49: 132 (1984)). Expressed fusion proteins were separated by SDS gel electrophoresis, excised from the gel, eluted and freeze dried. Rabbits were immunized by  
25 subcutaneous injection with 100 µg of the lyophilisate combined with Freund's adjuvant according to standard procedures. Immunization was repeated three times at two-week intervals using incomplete Freund's adjuvant. The rabbit was bled and antiserum was obtained. The obtained antiserum was depleted from antibodies reactive with *E. coli* and phages as described above and tested for reactivity against the renal carcinoma antigen as described for the human serum.  
30 Reactivity was detected at dilutions of 1: >100,000.

Additional clones were identified from pancreatic cancer tumor specimen using the SEREX method of Sahin et al., (1995). A cDNA library was prepared and reacted with high titer IgG in sera of pancreatic carcinoma patients. A total of  $8 \times 10^5$  clones were screened with autologous serum, and  $4.5 \times 10^3$  clones were screened with three different allogeneic sera. Twenty three clones, representing seven different transcripts were found. Four were previously unknown, unisolated genes. Of the remaining three, glycolytic enzyme aldolase A was found (SEQ ID Nos:799 and 800). Another molecule was "known" in that it was homologous to the rat eIF-5 gene (SEQ ID Nos:801 and 802), which is a eukaryotic translation initiation factor. The human eIF-5 gene was not previously known.

When hepatocellular carcinoma libraries were studied in the same way, a total of  $1.5 \times 10^6$  clones were screened, and 98 positives were found. A total of 59 of these were sequenced, and corresponded to at least 20 different transcripts. Nine of these were assayed with allogeneic sera from hepatocellular cancer (HCC) patients and normal patients. High titered antibody was restricted to HCC patients. The majority of isolated sequences did not correspond to known molecules. Three which did were human albumin (SEQ ID Nos:803 and 804), senescence marker protein SMP30 (SEQ ID NOs:805 and 806), and C3VS (SEQ ID NOs:807 and 808). The latter was overexpressed in 2 of 4 hepatocarcinoma tissues, as compared to normal. Expression of SMP30 was found to vary highly.

The methodology was combined with subtractive cDNA techniques when assaying leukemia cells (T-ALL). An antigen was found which was identical to a broadly expressed, DNA repair enzyme.

Further assays identified the known molecule galectin-9 (SEQ ID NOs:809 and 810), as being highly expressed on human macrophages and dendritic cells. Expression is upregulated during differentiation of monocytes to macrophages. Highest levels were found on monocyte derived, dendritic cells.

Fusion proteins "LD1-mFc" and "LD2-mFc" were constructed to help analyze galectin-9. These consist of murine IgG heavy chain fragments, and a lectin domain (LD1, or LD2), as the N-terminus. Analysis indicated that the C-terminal lectin domain binds to the surface ligands, while the cell surface ligands recognized by the C-terminal lectin domain of galectin-9 was expressed only in a small, subpopulation of dendritic cells.

Further analysis of ovarian cancer cells (500,000 clones, using the SEREX method described

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above), identified previously known antigens MAGE-4 (SEQ ID Nos:811 and 812) and restin (SEQ ID Nos:813 and 814), and six other newly identified molecules.

Further experiments were carried out which involved restin. A variation of restin is known, i.e., "CLIP170", which was reported to mediate binding of endosomes to microtubules. It was found that both restin and CLIP 170 are highly expressed in dendritic cells, and are involved in the formation and transport of macropinosomes, a feature of professional antigen presenting cells. Expression of restin was induced after 48 hours of culture of monocytes in GM-CSF/IL-4 supplemented medium. Highest levels were found in immature dendritic cells. When microtubule systems, which are essential for the activity of restin/CLIP-170 were disrupted, macropinocytosis was lost completely.

Further work with the methodology disclosed herein on glioma identified a clone encoding nm23-H2 protein (SEQ ID Nos:815 and 816). This clone corresponds to subunit B of nucleoside diphosphate kinase, which is implicated in tumor metastasis control. It is also known as PuF, a transcriptional factor, for c-myc proto-oncogenes. Antibodies against the protein were found in 1 of 18 sera of brain malignancy patients, 3 of 20 melanoma patients, and 2 of 20 sera from healthy patients. When expression studies were carried out using RT-PCR, 25 of 28 brain tumor, and 4 or 5 meningioma tumor samples were found to express the gene.

#### **Example 9: Isolation and analysis of lung cancer clones**

A cDNA library was constructed from a case of moderately differentiated adenocarcinoma of the lung, obtained from the Department of Pathology at The New York Hospital. The library was constructed in a  $\lambda$ ZAP Express vector using a cDNA library kit (Stratagene, La Jolla, CA).

The cDNA library was screened with autologous patient's serum as described previously [Sahin, U. et al., *Proc Natl Acad Sci USA* 92:11810-3 (1995); Chen, Y.T. et al. *Proc Natl Acad Sci USA*. 94:1914-8 (1997)]. Briefly, the serum was diluted 1:10, pre-absorbed with transfected *E. coli* lysate, and a 1:10 dilution of the absorbed serum (final dilution of serum 1:100) was incubated overnight at room temperature with the nitrocellulose membranes containing the phage plaques. After washing, the filters were incubated with alkaline phosphatase-conjugated goat anti-human Fc  $\gamma$  secondary antibodies and the reactive phage plaques were visualized by incubating with 5-bromo-4-chloro-3-indolyl-phosphate and nitroblue tetrazolium. Phagemid clones encoding human

immunoglobulin sequences were subsequently eliminated during the secondary screening.

The reactive clones were subcloned, purified, and *in vitro* excised to pBK-CMV plasmid forms (Stratagene). Plasmid DNA was prepared using Wizard Miniprep DNA Purification System (Promega, Madison, WI). The inserted DNA was evaluated by EcoRI-XbaI restriction mapping, and  
5 clones representing different cDNA inserts were sequenced. The sequencing reactions were performed by DNA Services at Cornell University (Ithaca, NY) using ABI PRISM (Perkin Elmer) automated sequencers.

To evaluate the mRNA expression pattern of the cloned cDNA in normal and malignant tissues, gene-specific oligonucleotide primers for PCR were designed to amplify cDNA segments of  
10 300-400bp in length, with the estimated primer melting temperature in the range of 65-70°C. All primers were commercially synthesized (Operon Technologies, Alameda, CA). RT-PCR were performed using 35 amplification cycles in a thermal cycler (Perkin Elmer) at an annealing temperature of 60°C.

Genomic DNA were extracted from cell lines and frozen tumor tissue. Following restriction  
15 enzyme digestion, the DNA was separated on a 0.7% agarose gel, blotted onto nitrocellulose filters, and hybridized to an  $^{32}\text{P}$ -labeled DNA probe at high stringency (65°C, aqueous buffer). Washing of the blot was also under high stringency conditions, with a final wash in 0.2XSSC with 0.2% SDS at 65°C.

To identify the 5' end of the mRNA transcripts, RACE (rapid amplification of cDNA ends)  
20 methodology was utilized using the Marathon cDNA amplification kit (Clontech) and adaptor-ligated testicular cDNA as the substrate. The PCR products, after separation by agarose gel electrophoresis, were cloned into the direct PCR cloning vector pGEM-T (Promega).

Single-strand conformation polymorphism (SSCP) analysis was performed to analyze cDNA from various tissues, using previously described protocols [Dracopoli, C.D. et al., New York: John  
25 Wiley and Sons, Inc. (1997)]. Briefly, PCR was performed with 5  $\mu\text{l}$  RT product in a final volume of 25  $\mu\text{l}$ , with 2  $\mu\text{Ci}$  of  $\alpha^{32}\text{P}$ -dCTP (~3000 Ci/mmol, New England Nuclear) per reaction. The PCR conditions was as described for RT-PCR above. After the PCR, 1  $\mu\text{l}$  of the mixture was diluted with 5  $\mu\text{l}$  of denaturing buffer (95% formamide, 20 mM EDTA, 0.05% bromophenol blue, 0.05% xylene cyanol), heat-denatured at 98°C for 2 min, and electrophoresed through an 8% polyacrylamide gel  
30 with 10% glycerol. As controls, aliquots of the same samples were diluted with a standard non-



denaturing DNA loading dye and electrophoresed in parallel. The electrophoresis was performed at room temperature at a constant power of 10-12 watts. The gel was then dried and autoradiography performed for 15-24 hours with an intensifying screen.

#### 5 Identification of Immunoreactive cDNA clones

A cDNA expression library of  $1.42 \times 10^7$  primary clones was prepared from Lu15, a specimen of moderately differentiated adenocarcinoma of the lung and  $8 \times 10^5$  phage plaques were immunoscreened with absorbed autologous patient serum at 1:100 dilution. Excluding false-positive clones encoding immunoglobulin gene fragments, 20 positive clones were identified. These clones  
10 were purified and sequence analyzed. Comparisons of the sequences showed that these clones represented cDNAs from 12 distinct genes, designated NY-LU-1 through NY-LU-12 (Table 9). A homology search through the GenBank/EMBO databases revealed that 4 of the 12 genes corresponded to previously known molecules, and 8 others were unknown genes, with sequence identity limited only to short segments of known genes or to expressed sequence tags (ESTs).

15

Table 9: NY-LU clones

Gene Designation	Gene/Sequence Identity [Accession Number]	cDNA	Comments
NY-LU-1	Aldolase A (N and H type) [X06352]	Lu-15/24, 72, 83, 158, 219, 241	Human fructose, 1,6 diphosphate aldolase A. Expressed in muscle (M type), but also in most other tissues (N and H types). Levels increased in most lung cancers; released into blood upon trauma and in several cancers.
20 NY-LU-2	hASNA-1 [U60276]	Lu-15/26, 66	Human homolog of the ATP-binding ars A component of the bacterial arsenite transporter. Previously cloned by SEREX from a testicular library (Chen et al., unpolished). Ubiquitously expressed.
NY-LU-3	Annexin IX [L19605]	LU-15/64	Homosapiens 56K autoantigen. Antibodies to Annexin IX are found in multiple autoimmune diseases. ubiquitously expressed.

NY-LU-4	Rip-1 [U55766]	Lu-15/65	Human HIV Rev-interacting protein. Expressed in B cells, monocytes and rhabdomyoma cells.
NY-LU-5	Unknown [W61291, W92962, etc.]	Lu-15/80	Expressed ubiquitously (by RT-PCR).
NY-LU-6	Unknown [none]	Lu-15/85	Sequence contains no ORF, expressed ubiquitously (by RT-PCR).
NY-LU-7	Unknown [W23466, AA167732, etc.]	Lu-15/135,217	Expressed in neuron, pregnant uterus, lung ca., parathyroid tumors, etc.
NY-LU-8	Unknown [Z78323, N39225, etc.]	Lu-15/139	Expressed in fetal heart, retin, multiple sclerosis, etc.
NY-LU-9	Unknown [W26569, AA036884, etc.]	Lu-15/145	Expressed in retina, pregnant uterus, fetal liver-spleen, etc.
NY-LU-10	Unknown [M29204, etc.]	Lu-15/154	Expressed in colon, pancreas, pregnant uterus, fibroblasts, etc.
NY-LU-11	Unknown [W23466, AA057400, etc.]	Lu-15/270	Expressed in retina, pregnant uterus, fetal heart, fetal liver-spleen, parathyroid tumors, etc.
NY-LU-12	g16	Lu-15/251	Located at the 3p21 TSG locus (see text)

Of the 4 known genes, aldolase A (NY-LU-1; SEQ ID NOs:689 and 690) was most frequently isolated, representing 6 of 20 primary positive clones in the entire screening. NY-LU-2 (SEQ ID NO:691), represented by two isolates, was the human homolog of the ATP-binding arsa component of the bacterial arsenite transporter, a gene which has been shown to be ubiquitously expressed in various tissues [Kurdi-Haidar, B. et al., *Genomics* 36:486-91 (1996)]. NY-LU-3 (SEQ ID Nos:692 and 693) encodes annexin XI, which is a 56KD ubiquitously expressed antigen to which autoantibodies have been described in sera from patients with various autoimmune diseases [Misaki, Y. et al., *J Biol Chem* 269:4240-6 (1994); Misaki, Y. et al., *J Rheumatol.* 22:97-102 (1995)]. The last gene in this group, NY-LU-4 (SEQ ID NOs:694 and 695), codes for the human HIV Rev interacting protein Rip-1, which has been shown to be expressed in the monocyte cell line U937, the rhabdomyoma cell line RD, as well as in adherent monocytes and primary lymphocytes [Refaeli, Y.

et al., *Proc Natl Acad Sci USA* 92:3621-5 (1995)].

Of the eight unknown genes, 6 (NY-LU-5, 7, 8, 9, 10, 11; SEQ ID Nos:696, 698, 699, 700, 701 and 702/703, respectively) shared sequence identify with reported expressed sequence tags (EST) , likely representing cDNA products derived from the same genes. These ESTs were derived from various somatic tissues unrelated to lung, e.g., neuron, pregnant uterus, colon, endothelial cells, etc., suggesting that these genes are widely expressed in human tissues (Table 9), making them unlikely candidates for vaccine-based tumor immunotherapy. These clones were not further investigated. The only novel gene in this group, NY-LU-6 (SEQ ID NO:697), showed no sequence identity to deposited sequences in the public databases. The tissue expression pattern of this gene was evaluated by RT-PCR analysis using gene-specific primers and a normal tissue RNA panel consisting of lung, colon, kidney, liver, brain and testis. Results showed universal expression in these tissues, and this clone was not further analyzed.

NY-LU-12 is on TSG locus of chromosome 3p21.

The last gene in the unknown gene group, NY-LU-12, was represented by the immunoreactive clone Lu15-251. This clone, 1081bp in length, contained an uninterrupted open reading frame (ORF) of 952 bp, followed by a 129bp 3'untranslated region. No translation initiation codon was identified, indicating that this was a partial cDNA clone.

A sequence homology search revealed that this gene shared up to 30% homology with two different human proteins at its C-terminus (Fig. 1), LUCA15 and DXS8237E (GenBank accession numbers U23946, and P98175) and also shared homology to S1-1, the rat counterpart of DXS8237E [Inoue, A. et al., *Nucleic Acids Res.* 24:2990-7 (1996)]. LUCA15 was subsequently proven to be a gene immediately centromeric to NY-LU-12 on the TSG locus on chromosome 3p21 (see below and [Wei, M.H. et al., *Cancer Res.* 56: 2487-92 (1996)]). Our analysis of LUCA15 revealed the presence of a nuclear localization signal in the putative LUCA15 protein. DXS8237E, was located on chromosome Xp11.23 [Coleman, M.P. et al., *Genomics* 31:135-8 (1996)] and its rat homolog, S1-1, has been shown to be an RNA-binding protein [Inoue, A. et al., *Nucleic Acids Res.* 24:2990-7 (1996)].

Of particular interest, however, was that a short segment (92bp) at the 5' end of NY-LU-12 was identical to a previously identified gene, g16 (GenBank accession number U50839), which was

mapped to chromosome 3p21.3 and was interrupted in the small cell lung cancer line NCI-H740.

To compare NY-LU-12 with g16, the full-length NY-LU-12 cDNA sequence was obtained from normal testicular mRNA through a combination of 5'RACE and direct PCR cloning strategies.

The predominant cDNA form (SEQ ID No:707), excluding the poly A tail, is of 3591bp in length.

5 An open-reading-frame of 1123 amino acid residues (SEQ ID No:708) was identified (nt. 102-3470), with 101bp of 5' untranslated and 129bp of the 3' untranslated region. The nucleotide and amino acid sequences are shown in Fig. 2.

Comparison with the g16 sequence verified that these two are identical genes and mapped NY-LU-12 to *TSG* locus on 3p21. However, the reported g16 sequence, 2433 bp in length, lacks the  
10 5' end 110 bases which include the translational initiation codon at nucleotide 102, and also the 3' end 980 nucleotides of NY-LU-12. In addition, 74bp DNA segment (nt. 1587-1659 of NY-LU-12) was absent in the reported g16 sequence. Oligonucleotide primers flanking this 74 bp region were designed and used to amplify RNA from 1 normal lung, 5 lung cancer cell lines, and 6 lung cancer specimens. Two RT-PCR products were seen in every specimen, corresponding to the sizes of the  
15 two cDNA variants. It was thus concluded that this variation represents an alternate splicing event which occurs in both normal and cancerous lung tissues. Of interest, however, was the difference in the putative translational products resulting from this additional 74bp exon. In the absence of this exon, the open-reading-frame of NY-LU-12 would end in the termination codon at nt.1736, as reported for g16, with a total length of 520 amino acid residues (in contrast to 1123 residues in the  
20 longer transcript). Moreover, this shorter form would not encode the C-terminal portion of the NY-LU-12 protein, the segment responsible for the immunoreactivity of Lu15-251 to the autologous patient serum.

#### Additional cDNA variants of NY-LU-12

25 In the process of 5'RACE cloning of the full-length NY-LU-12, three minor forms of cDNA products were identified which varied in their transcriptional initiation site and in their exon usage in the 5' segment of this gene. These variants will be described as transcripts B, C, and D (SEQ ID Nos:709, 711 and 712). Fig. 3 shows the comparison of these transcripts to the predominant cDNA form (transcript A, see Fig. 2).

30 Transcript B (Fig. 3A, bottom) contains an additional exon of 208 base pairs, inserted at

nucleotide 145 of the NY-LU-12 sequence. The original ORF of NY-LU-12 is disrupted due to this inserted sequence, and the AUG initiation codon used by transcript A is thus unlikely to be used by this transcript. A new potential translational initiation site, however, is found within this new exon and would continue the translation into the ORF of transcript A. The final product would be a protein of 1177 amino acids (SEQ ID NO:710), with the 69 residues at the N-terminus different from transcript A. Interestingly, this new exon encodes for a signal peptide not present in the transcript A (Fig. 3A, bottom), and it is possible that these two products are localized to different subcellular compartments.

Similar to transcript B, transcripts C and D both contained additional exon(s) not present in transcript A. Transcript C contained two extra exons in tandem and a length of 364bp, only one of which (137bp) was present in transcript D, Figure 3B. These extra exon(s), inserted at the same alternate splicing site as transcript B, disrupted the original ORF, and the only long ORF would initiate at nucleotide position 498 of NY-LU-12 (959 of transcript C, 635 of transcript D).

Considering the long untranslated region at the 5' end, it is doubtful whether transcripts C and D are indeed translated *in vivo*.

Correlating with this variation of NY-LU-12 mRNA, Northern blot analysis showed several RNA species in normal tissues, ranging approximately from 3 to 4.4 Kb. The intensity of individual bands also appear to vary among different tissues, suggesting post-transcriptional tissue specific regulation of NY-LU-12 mRNA.

#### Features of NY-LU-12 and its putative gene product

Analysis of the NY-LU-12 amino acid sequence showed 20 inexact 6 amino acid repeats with a consensus sequence of D(F/Y)RGR(D/E) close to the N-terminus (Fig. 2). These repeats were separated by 4 to 6 amino acid intervals, which showed no apparent sequence homology among each other. This feature in primary sequence is distinctive among known proteins.

Hydrophilicity plot revealed that this region, although hydrophilic in general, has regular hydrophobic turns, and these cycles of hydrophilicity changes correspond to the hexapeptide repeats. Although the significance of this characteristic is unclear at present, this segment of sequence is highly rich in arginine and aspartic acid, a feature shared by RNA binding proteins. Similar motifs, rich in arginine and aspartic acid residues, were found in other RNA-binding proteins [Witte, M.M.

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et al., *Proc Natl Acad Sci USA* 94: 1212-7 (1997); Wilson, R. et al., *Nature* 368:32-8 (1994); Seraphin, B. et al., *Nature* 337:84-7 (1989); Takagaki, Y. et al., *Proc Natl Acad Sci USA* 89:1403-7 (1992)], e.g., RNA [Seraphin, B. et al., *Nature* 337:84-7 (1989)] hnRNA 3' end cleavage stimulation factor [Takagaki, Y. et al., *Proc Natl Acad Sci USA* 89:1403-7 (1992)], etc., indicating that NY-LU-12 is likely to be an RNA-binding protein. Consistent with this, PROSITE analysis of the putative NY-LU-12 protein identified a bipartite nuclear localization signal between amino acids 1016-1032 and a 4-residue nuclear localization pattern (PRKR) at amino acid 604-607 (Fig. 2), suggesting that NY-LU-12 is a nuclear protein. Analysis for post-translational modification sites showed potential sites for tyrosine sulfation, amidation, as well as phosphorylation sites for protein kinase A, C, casein kinase II, and tyrosine kinase. A PEST region, peptide sequences consistently found among unstable proteins with short half lives, was identified at amino acids 897-928 (Fig. 2), implying NY-LU-12 as an unstable protein.

#### Southern blot analysis of NY-LU-12 in normal and tumor tissues

To investigate the status of NY-LU-12 in normal and tumor cells, Southern blot analysis was performed on 9 lung cancer cell lines (3 adenocarcinoma, 2 squamous, and 3 large cell anaplastic), Lu15 tumor DNA, and a colon cancer cell line HT29 (Fig. 4). (HT29 was included due to the finding of an EST identified in the GenBank, accession number AA079461, which appeared to be a fusion sequence between semaphorin IV gene and NY-LU-12.) Using a 1.1Kb cDNA probe (nucleotide 1095-2140) and HindIII digested DNA, the results showed that one of the two hybridizing bands was absent in NCI-H740, confirming that NY-LU-12 was partially deleted in this cell line. The breakpoint of this deletion, by using primers from different regions, was further defined to be between nucleotides 1433 and 1777 of NY-LU-12, with the 3' sequences homozygously deleted. Besides NCI-H740, however, no evidence of homozygous deletion was seen in any other tumor cell line sample or in LU15. The similar band intensities and identical sizes of the DNA signals in all specimens also argued against the possibility of a heterozygous deletion or translocation of this gene, at least in the region analyzed. No change was found in HT29, suggesting that the semaphorin IV/NY-LU-12 fusion sequence in the GenBank probably represents a cloning artifact.

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SSCP and sequence analysis of NY-LU-12 in Lu15 tumor DNA.

The mapping of NY-LU-12 to the lung cancer *TSG* locus raised the possibility that an altered protein product due to mutational event may be the basis for the autologous immune recognition. This possibility was explored using DNA sequencing and single-strand confirmational polymorphism (SSCP) analysis.

The DNA sequence contained in the immunoreactive clone Lu15-251 (nucleotide 2518-3599 of NY-LU-12) was obtained from the normal counterpart by RT-PCR cloning using autologous normal lung tissue, and no mutations were found when compared to Lu15-251.

RT-PCR SSCP was then used to analyze the entire NY-LU-12 gene, comparing Lu15 tumor tissue and autologous normal lung tissue. To encompass the whole sequence, 10 sets of primer pairs were designed, each amplifying a range of 205 to 603 bps. For products >400bps, a restriction enzyme digestion step was added prior to the electrophoresis step to further reduce the fragment sizes and increase the assay sensitivity. Results showed no reproducible changes between normal and tumor tissues, and thus no evidence of mutation in Lu15 tumor cDNA. A representative set of SSCP analysis is shown in Fig. 5.

Serological response to NY-LU-12 in lung cancer patient

The frequency of anti-NY-LU-12 response was examined among normal adult and patient sera using the phage plaque assay identical to the original immunoscreening procedure. Of 21 absorbed sera from allogeneic lung cancer patients, one (Lu22) reacted strongly with the Lu15-251 plaque at 1:1000 dilution, and another (Lu7) also reacted at 1:1000, but only weakly. Nineteen other lung cancer patient sera were non-reactive, nor were the sera from 16 healthy donors, 15 colon cancer, 5 breast cancer, 1 renal cancer, 1 prostate cancer, 1 esophageal cancer, and 1 melanoma patients.

Example 10: Expression analysis of additional cancer associated nucleic acids

The clone RING 3 was isolated from breast SEREX analysis as LONY-Br-5 (see above). The gene was identified as homologous to the "bromodomain testis" gene (BRDT; GenBank accession number AF019085). Analysis of related genes identified BRDT as a gene expressed only in testis, which was then investigated by RT-PCR analysis as described above.

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The primers used to perform RT-PCR had the following sequences:

BRDT F1: CAAGAAAGGCACTCAACAG (bp 543-563 of BRDT)

BRDT R1: TTCACTACTTGCTTTAACTGC (bp 776-797 of BRDT)

The meiotic protein H1T (Histone 1 Testis; GenBank accession number M60094) was  
5 identified through a literature search for meiotic proteins (testis specific expression).

The primers used to perform RT-PCR had the following sequences:

H1F1: TGCCGAACCTCTCTGTGTC (bp 116-135 of H1T)

H1R1: GCTTCGTGTAGATTTAGGAATC (bp 344-366 of H1T)

10 Table 10: RT-PCR analysis

	<u>Normal Tissue</u>	<u>BRDT</u>	<u>H1T</u>
	mammary gland	-	-
	liver	-	-
15	small intestine	-	-
	brain	-	+/- (very weak)
	lung	-	-
	fetal brain	-	-
	placenta	+	+
20	kidney	-	-
	skeletal muscle	-	-
	pancreas	-	-
	adrenal gland	-	-
	heart	-	-
25	thymus	-	-
	uterus	-	-
	prostate	-	+/- (very weak)
	spleen	-	-
	Testis	+	+

30

	<u>Tumor Tissue</u>	<u>BRDT</u>	<u>H1T</u>
	Colon	0/6	0/6
35	Breast	0/6	6/6+
	Melanoma	0/12	3/12+
	Lung	8/26+	4/26+
	Renal	0/2	0/2
	Ovary	0/2	0/2
40	Esophageal	0/1	0/1



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Gastric	0/1	0/1
Bladder	0/2	0/2

Lung cancer specific expression of BRDT was observed (see table above). BRDT was expressed only in normal testis and possibly in placenta. The expression analysis of H1T revealed that all breast tumor samples (6 of 6) and ~30% lung cancers and melanoma tissue samples expressed H1T. H1T was expressed in normal testis and possibly in placenta and brain.

### **Example 11: allogeneic serotyping**

To confirm the cancer associated expression of SEREX clones, allogenic sera screening of gastric cancer patients' sera was conducted. Sera from normal patients (gastritis) was used as a control for expression of the clones in non-gastric cancer. The screening procedure used was as described above for the SEREX screening, except for the absorption of anti-bacterial and anti-bacteriophage antibodies. The modifications were as follows.

Serum from a stomach cancer patient or a normal individual was diluted to 1:10 in TBS (Tris buffered saline; final volume 5 ml) and passed through a column (BIO-RAD Poly-Prep Chromatography Column, Hercules. CA, USA) containing 0.5 ml Sepharose-4B cross linked to E. coli Y1090 lysate and 0.5 ml Sepharose-4B cross linked to E. coli BNN97 (5 Prime 3 Prime, Inc, Boulder, CO, USA). After repeating the column chromatography 10 times, serum was then diluted to 1:100 in TBS containing 1% BSA and 0.02% sodium azide. To remove antibodies to bacteria and bacteriophages further, 10 ml absorbed serum was incubated overnight with a 82 mm nitrocellulose membrane on which XL-1 Blue MRF' bacteria and lambda ZAP Express phages (Stratagene, La Jolla, CA USA) were immobilized. The serum was stored at - 80°C until use. For allogeneic typing, an equal numbers of positive phage and negative phage were mixed and plated and processed by the standard SEREX screening procedure.

The results of the allogenic screening experiments follow:

**Table 11: Allogenic Sera Screening of SEREX Sequences from Gastric Patients**

Sequence		Isolated in Serex Patients	Allogenic Serotyping Gastric Cancer Sera	Allogenic Serotyping Normal Sera
Gene/Clone	Number			
RPB-J H-2K binding factor		SM1	6/12	6/16
5 Telomeric repeat binding protein		SM1	1/12	0/16
Ser/Thr protein kinase		SM1	1/12	0/16
SR Y interacting protein-1		SM1	2/12	1/16
Sterol carrier protein X		SM1	2/12	0/16
10 Archain		SM1	1/12	1/16
HEM-1		SM1	2/12	1/16
Id-1 helix-loop-helix protein		SM1	1/12	0/16
15 helix-loop-helix transcription factor		SM1	1/12	0/16
Follistatin related precursor protein		SM1,CK, KM	6/12	0/16
Translation initiation factor eIF-4gamma		SM1,SS1, KM	5/12	2/16
20 M phase phosphoprotein I		SM1,SS1	8/12	5/16
Lysal tRNA synthase		SM1	1/12	0/16
Gelsolin		SM1	4/12	0/16
Zinc finger protein		SM1	1/12	1/16
Goliath		SM1	2/12	1/16
25 zhx-1		SM1	1/12	1/16
SG24		SM1,SS1, KM	5/12	0/16
SG132		SM1	3/12	0/16
S553		SM1	7/12	7/16
S134		SM1	3/12	0/16
30 S328		SM1	2/12	1/16
S365		SM1, KM	2/12	0/16

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5	FKBP25		KM, SS1	5/12	0/16
	Pros-27		KM, CK	3/12	1/16
	BS4		KM	1/12	1/16
	GnRH-II		KM	1/12	0/16
	CTBP		KM	1/12	0/16
10	ETF		KM	3/12	1/16
	KIAA0438		KM	1/12	5/16
	KIAA0367		KM	4/12	3/16
	APK1		KM	2/12	0/16
	IPP		KM	1/12	0/16
15	Tropomyosin		KM	1/12	0/16
	p63		KM	1/12	0/16
	KIAA0181		KM	1/12	0/16
	KIAA0349		KM	1/12	0/16
	RPB1		KM	5/12	9/15
20	PPIM		KM	1/12	-
	EB virus		KM	3/12	-
	G.KM073		KM	6/12	-
	G.KM403		KM	1/12	-
	KM192		KM	1/12	-
25	KM294		KM	1/12	-
	KM362		KM	1/12	-
	KM031		KM	1/12	-
	KM081		KM	3/12	-
	KM201		KM	1/12	-
30	KM1496		KM	1/12	-
	KM334		KM	1/12	-
	KM313		KM	1/12	-
	E-cad/Y		CK	1/12	0/16
	IPBP		SS1	1/4	-
	OS-9		SS1	1/4	-

Kinesin light chain		SS1	1/4	-
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The screening results shown above confirm the association of the SEREX clones with cancer. There is a higher correlation of cancer and the expression of certain clones, in particular, follistatin related precursor protein, the translation initiation factor eIF-4gamma, the unknown sequence SG24, the FK506-binding protein 25, and the unknown sequence G.KM073. These clones are well suited to serve as diagnostic indicators of disease and as targets for therapeutics (e.g., vaccine compositions) development.

#### 10 **Example 12: Preparation of recombinant cancer associated antigens**

To facilitate screening of patients' sera for antibodies reactive with cancer associated antigens, for example by ELISA, recombinant proteins are prepared according to standard procedures. In one method, the clones encoding cancer associated antigens are subcloned into a baculovirus expression vector, and the recombinant expression vectors are introduced into appropriate insect cells. Baculovirus/insect cloning systems are preferred because post-translational modifications are carried out in the insect cells. Another preferred eukaryotic system is the *Drosophila* Expression System from Invitrogen. Clones which express high amounts of the recombinant protein are selected and used to produce the recombinant proteins. The recombinant proteins are tested for antibody recognition using serum from the patient which was used to isolated the particular clone, or in the case of cancer associated antigens recognized by allogeneic sera, e.g. certain breast cancer and gastric cancer associated antigens, by the sera from any of the patients used to isolate the clones or sera which recognize the clones' gene products.

Alternatively, the cancer associated antigen clones are inserted into a prokaryotic expression vector for production of recombinant proteins in bacteria. Other systems, including yeast expression systems and mammalian cell culture systems also can be used.

#### **Example 13: Preparation of antibodies to cancer associated antigens**

The recombinant cancer associated antigens produced as in Example 12 above are used to generate polyclonal antisera and monoclonal antibodies according to standard procedures. The antisera and antibodies so produced are tested for correct recognition of the cancer associated

antigens by using the antisera/antibodies in assays of cell extracts of patients known to express the particular cancer associated antigen (e.g. an ELISA assay). These antibodies can be used for experimental purposes (e.g. localization of the cancer associated antigens, immunoprecipitations, Western blots, etc.) as well as diagnostic purposes (e.g., testing extracts of tissue biopsies, testing for the presence of cancer associated antigens).

**Example 14: Expression of cancer associated antigens in cancers of similar and different origin.**

The expression of one or more of the cancer associated antigens is tested in a range of tumor samples to determine which, if any, other malignancies should be diagnosed and/or treated by the methods described herein. Tumor cell lines and tumor samples are tested for cancer associated antigen expression, preferably by RT-PCR according to standard procedures. Northern blots also are used to test the expression of the cancer associated antigens. Antibody based assays, such as ELISA and western blot, also can be used to determine protein expression. A preferred method of testing expression of cancer associated antigens (in other cancers and in additional same type cancer patients) is allogeneic serotyping using a modified SEREX protocol (as described above for gastric clones).

In all of the foregoing, extracts from the tumors of patients who provided sera for the initial isolation of the cancer associated antigens are used as positive controls. The cells containing recombinant expression vectors described in the Examples above also can be used as positive controls.

The results generated from the foregoing experiments provide panels of multiple cancer associated nucleic acids and/or polypeptides for use in diagnostic (e.g. determining the existence of cancer, determining the prognosis of a patient undergoing therapy, etc.) and therapeutic methods (e.g., vaccine composition, etc.).

**Example 15: HLA typing of patients positive for cancer associated antigen**

To determine which HLA molecules present peptides derived from the cancer associated antigens, cells of the patients which express the cancer associated antigens are HLA typed. Peripheral blood lymphocytes are taken from the patient and typed for HLA class I or class II, as

well as for the particular subtype of class I or class II. Tumor biopsy samples also can be used for typing. HLA typing can be carried out by any of the standard methods in the art of clinical immunology, such as by recognition by specific monoclonal antibodies, or by HLA allele-specific PCR (e.g. as described in WO97/31126).

5

**Example 16: Characterization of breast cancer associated antigen peptides presented by MHC class I and class II molecules.**

Antigens which provoke an antibody response in a subject may also provoke a cell-mediated immune response. Cells process proteins into peptides for presentation on MHC class I or class II molecules on the cell surface for immune surveillance. Peptides presented by certain MHC/HLA molecules generally conform to motifs. These motifs are known in some cases, and can be used to screen the breast cancer associated antigens for the presence of potential class I and/or class II peptides. Summaries of class I and class II motifs have been published (e.g., Rammensee et al., *Immunogenetics* 41:178-228, 1995). Based on the results of experiments such as those described in Example 15, the HLA types which present the individual breast cancer associated antigens are known. Motifs of peptides presented by these HLA molecules thus are preferentially searched.

One also can search for class I and class II motifs using computer algorithms. For example, computer programs for predicting potential CTL epitopes based on known class I motifs has been described (see, e.g., Parker et al., *J. Immunol.* 152:163, 1994; D'Amaro et al., *Human Immunol.* 43:13-18, 1995; Drijfhout et al., *Human Immunol.* 43:1-12, 1995). HLA binding predictions can conveniently be made using an algorithm available via the Internet on the National Institutes of Health World Wide Web site at URL <http://bimas.dcrt.nih.gov>. Methods for determining HLA class II peptides and making substitutions thereto are also known (e.g. Strominger and Wucherpennig (PCT/US96/03182)).

The lung cancer SEREX clone polypeptides NY-LU-12 and NY-LU-12B (variant B), SEQ ID NOs: 708 and 710, were subjected to the HLA binding peptide analysis described above, using the NIH website, to identify HLA binding peptides for several common HLA molecules (HLA-A1, A2, A3, A24, B7, B44, and B52). The results are listed below in Table 12.

Table 12: Identification of HLA binding peptides in lung SEREX clones

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		amino acids of		
HLA	peptide	NY-LU-12 protein	SEQ ID NO	
5	A1	NVEE-HSFSY	67 - 75	713
		PVDP-NILDY	287 - 295	714
		DTDY-RSMEY	398 - 406	715
10	A2	SLLE-DAIGC	506 - 514	716
		TLMI-QDKEV	521 - 529	717
		YVSSLDFWYC	533 - 542	718
		VIVEVLEPYV	671 - 680	719
		KLTD-WNKLA	948 - 956	720
		QLSDLHKQNL	975 - 984	721
		KQSEQELAYL	991 - 1000	722
		KLVDKEDIDT	1042 - 1051	723
15		VMFA-RYKEL	1114 - 1122	724
20	A3	QMFG-YGQSK	417 - 425	725
		GMPVKNLQLK	481 - 490	726
		GLPE-EEEIK	823 - 831	727
		LLCRRQFPNK	958 - 967	728
25	A24	EYRD-VDHRL	405 - 413	729
		GYVC-VEFSL	499 - 507	730
		DYGY-VCVEF	497 - 505	731
		WYCKRCKANI	540 - 549	732
		TYPQPQKTSI	574 - 583	733
		IYRSTPPEVI	663 - 672	734
		HYYQ-GKKYF	754 - 762	735
		VYVP-QDPGL	816 - 824	736
30	B7	WNRDYPPPPL	26 - 35	737
		MPPV-DPNIL	285 - 293	738
		TARD-AQRDL	432 - 440	739
		GPSEEKPSRL	448 - 457	740
35		TPPEVIVEVL	667 - 676	741
		RVMFARYKEL	1113 - 1122	742
40	B44	REMG-SCMEF	272 - 280	743
		EEQSSDAGLF	376 - 385	744
		KEYN-TGYDY	490 - 498	745
		TEAKQELITY	566 - 575	746
		VEALRVVKIL	710 - 719	747
		GEYG-GDSY	906 - 914	748
		LERREREGKF	1000 - 1009	749

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B52	RQDGESKTIM	650 - 659	750
	TPPEVIVEVL	667 - 676	751
	YGFIDLD SHV	701 - 710	752
	RQFP-NKEVL	962 - 970	753

5

## NY-LU-12B (variant B)

10	A1	NVEE-HSFSY	121 - 129	754
		PVDP-NILDY	341 - 349	755
		DTDY-RSMEY	452 - 460	756
15	A2	WQSA-RFY YL	41 - 49	757
		SLLE-DAIGC	560 - 568	758
		TLMI-QDKEV	575 - 583	759
		YVSSLD FWYC	587 - 596	760
		VIVEVLEPYV	725 - 734	761
		KLTD-WNKLA	1002 - 1010	762
		QLSDLHKQNL	1029 - 1038	763
20		KQSEQELAYL	1045 - 1054	764
		KLVDKEDIDT	1096 - 1105	765
		VMFA-RYKEL	1168 - 1176	766
25	A3	QMFG-YGQSK	471 - 479	767
		GMPVKNLQLK	535 - 544	768
		GLPE-EE EIK	877 - 885	769
		LLCRRQFPNK	1012 - 1021	770
30	A24	YYLN-ATDVL	47 - 55	771
		FYYLNATDVL	46 - 55	772
		EYRD-VDHRL	459 - 467	773
		GYVC-VEFSL	553 - 561	774
		DYGY-VCVEF	551 - 559	775
		WYCKRCKANI	594 - 603	776
35		TYPQPQKTSI	628 - 637	777
		IYRSTPPEVI	717 - 726	778
		HYYQ-GKKYF	808 - 816	779
		VYVP-QDPGL	870 - 878	780
40	B7	WNRDYP P PPL	80 - 89	781
		MPPV-DPNIL	339 - 347	782
		TARD-AQRDL	486 - 494	783
		GPSEEKPSRL	502 - 511	784
		TPPEVIVEVL	721 - 730	785
45		RVMFARYKEL	1167 - 1176	786



5	B44	SEAWSSNEKF	59 - 68	787
		REMG-SCMEF	326 - 334	788
		EEQSSDAGLF	430 - 439	789
		KEYN-TGYDY	544 - 552	790
		TEAKQELITY	620 - 629	791
		VEALRVVKIL	764 - 773	792
		GEYG-GDSY	960 - 968	793
		LERREREGKF	1054 - 1063	794
10	B52	RQDGESKTIM	704 - 713	795
		TPPEVIVEVL	721 - 730	796
		YGFIDLDHV	755 - 764	797
		RQFP-NKEVL	1016 - 1024	798

15 Likewise, other clones identified herein can be analyzed for the presence of candidate HLA binding peptides using no more than routine experimentation.

**Example 17: Identification of the portion of a cancer associated polypeptide encoding an antigen**

20 To determine if the cancer associated antigens isolated as described above can provoke a cytolytic T lymphocyte response, the following method is performed. CTL clones are generated by stimulating the peripheral blood lymphocytes (PBLs) of a patient with autologous normal cells transfected with one of the clones encoding a cancer associated antigen polypeptide or with irradiated PBLs loaded with synthetic peptides corresponding to the putative protein and matching

25 the consensus for the appropriate HLA class I molecule (as described above) to localize an antigenic peptide within the cancer associated antigen clone (*see, e.g., Knuth et al., Proc. Natl. Acad. Sci. USA* 81:3511-3515, 1984; van der Bruggen et al., *Eur. J. Immunol.* 24:3038-3043, 1994). These CTL clones are screened for specificity against COS cells transfected with the cancer associated antigen clone and autologous HLA alleles as described by Brichard et al. (*Eur. J. Immunol.* 26:224-230,

30 1996). CTL recognition of a cancer associated antigen is determined by measuring release of TNF from the cytolytic T lymphocyte or by <sup>51</sup>Cr release assay (Herin et al., *Int. J. Cancer* 39:390-396, 1987). If a CTL clone specifically recognizes a transfected COS cell, then shorter fragments of the cancer associated antigen clone transfected in that COS cell are tested to identify the region of the gene that encodes the peptide. Fragments of the cancer associated antigen clone are prepared by

exonuclease III digestion or other standard molecular biology methods. Synthetic peptides are prepared to confirm the exact sequence of the antigen.

Optionally, shorter fragments of cancer associated antigen cDNAs are generated by PCR. Shorter fragments are used to provoke TNF release or  $^{51}\text{Cr}$  release as above.

5 Synthetic peptides corresponding to portions of the shortest fragment of the cancer associated antigen clone which provokes TNF release are prepared. Progressively shorter peptides are synthesized to determine the optimal cancer associated antigen tumor rejection antigen peptides for a given HLA molecule.

10 A similar method is performed to determine if the cancer associated antigen contains one or more HLA class II peptides recognized by CTLs. One can search the sequence of the cancer associated antigen polypeptides for HLA class II motifs as described above. In contrast to class I peptides, class II peptides are presented by a limited number of cell types. Thus for these experiments, dendritic cells or B cell clones which express HLA class II molecules preferably are used.

15

#### EQUIVALENTS

Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein. Such equivalents are intended to be encompassed by the following claims.

20 All references disclosed herein are incorporated by reference in their entirety.

We claim:

## TABLE 1

## SEQ ID NO. 1:

- 5 U72994, AC004022, Z68323, AE001160, L34078, AF064863, AC002132, U60440, X66494, N21242, AA678312, W86762, R01605, AA782843, AA275156, W41927, AA874648, AA571241, AA562747, W10480, AA451301, AA866631, AA466667, AA999057, AI029140.

## 10 SEQ ID NO. 2:

AC004022, U72994, AC002420, AC004125, AA690961, W41927, AA874648. AC004022, U72994, AC002420, AC004125, AA690961, W41927, AA874648.

15

## SEQ ID NO. 3:

- X98371, AL009008, L31790, Z83220, X92946, AC003975, AF008916, U80460, X75544, X66732, X95275, X52177, X07976, AC004451, Z74307, AB000878, AL009179, AF038667, 20 Z78544, Z48008, U23486, J05096, AB000882, Z30213, L11593, U18530, L27325, AC005191, M99579, AA130270, AA158245, AA903098, AI018453, AA436455, AA980593, AA172479, AA637487, AA116588, AA426854, AA050404, AA390025, AI006618, AI048382, C85944, AA673480, AI006510, AA823338, AA413694, W35075, AA015033, AA413584, W29693, AA637069, AA619839, AA125149, AA039004, AA674696, AA871138, AA414747, 25 AA198099, C91478, F071359, AA925957, AA820054, H16496, AI043756, AA892435, AA893551, AA818669, AA892785, AA944026, D33919, N96570, F19798, AI045451, AA800662, D65187, AA944025, AA925731, AA892314, AA945449.

## 30 SEQ ID NO. 4:

AA900930, AA925665.

## 35 SEQ ID NO. 5:

- U58105, Z81485, Z54236, Z48584, U61375, M55267, M59856, X51942, U77302, Z48621, AF032455, Z11866, AB013392, L32792, AA871997, AA084083, AA130829, AA083063, AA666290, N38894, D54459, T28921, AA806015, AA512059, AI043087, AI042894, 40 AA968324, AA238493, AA237462, AI042885, AI046424, AI035670, AA269430, AA250621, AI035540, AA260613, AA106870, AA238658, AA106134, AI042683, AA105958, AA144007, AA986558, AA457910, AA389400, AA673056, AA153254, AA754678, AI021109, AA390813, C36687, T41571, AI011183, AI013356, AI011739, AI030260, AA924384, C44421.

45

## SEQ ID NO. 6:

AF036717, U91327, AF036718, U56248, Z48795, Z99290, M30697, U58204, M24417, AF022983, M33581, AC004619, H64641, AA477478, AA369676, AA088359, AA057574,

AA683066, AA446279, AA332363, T09328, R80982, AA069486, AA410842, C18527,  
AA293033, H12730, AA287344, AA029631, R83063, AA061290, AA185993, AA880204,  
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5 AA924623, D47525, Z30723, AA897884, AA042465, AI009871, AA875198, C83016.

## SEQ ID NO. 7:

10 X74116, AL022148, AC004548, AC000352, Z11664, Z78065, Z74028, AE000163, AE000750,  
X74229, D90700, R59414, AA176708, W02568, AA354664, R43017, AA973553, F10008,  
D61827, AA826300, Z41398, T77572, R40189, H85823, W86541, T17276, AA679337,  
X83357, AA184845, AA416260, AA475603, AA388692, AA764445, AA388689, AA219880,  
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15 AA793690, AA619447, AA062257, AA522026, AA816247, AA892032, AA817702, H33461,  
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AA891755, AA698227, AA892782, AA899328, T04373, AA567522, AA698408, AA202615,  
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## SEQ ID NO. 8:

U08218, L38909, Y11095, AC002431, Z23069, S77418, U39060, L38580, AF053367, Z36506,  
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25 AA626429, F00559, AA604528, AA383348, AA040127, N84965, D54884, D54883, R94309,  
AA373184, AA128091, W68194, H58283, R76347, AA343938, AA305144, AI049611,  
AA384516, AA720553, N57395, R97387, D52674, AA169408, H66293, AA456362, T74258,  
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35 C64685, AA851367, C91730, AA143899, T23399.

## SEQ ID NO. 9:

40 AP000056, U43491, Z74919, L81498, Z94054, AC002503, L81499, AA740188, AA630241,  
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AA208416, AA959219, AA276381, W10055, AA462844, AA444278, W13447, W97802,  
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45 AA848674, AA924440, T15031, AA451569, H35524.

## SEQ ID NO. 10:

U25640, AA127328, H24207, H08275, AA283063, AA826096, AA417382, AA464874, W05562, AA453370, N51211, AA495859, R33871, H00927, AA623997, AA220442, AA178568, AA605493, AA394557, AA956116, AA999037, AA818246.

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SEQ ID NO. 11:

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SEQ ID NO. 12:

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SEQ ID NO. 13:

X94232, U90437, AC003052, U59809, AC004001, M95396, Z67884, X77486, U70051, 40 X14805, AF022976, Z83823, X77485, J04171, AF036007, U05768, U88315, Z98048, AF036009, AC005179, U41277, U32517, AE001138, D64060, M84387, H29022, AA814221, N26314, AA935912, AA873506, AA608576, AA453605, AA232674, Z38725, AA772022, AA025212, AA318330, R48115, AA234084, H18508, N64543, AA970508, R36933, AA306944, H49559, AA325555, H85834, H89988, AA343974, AA648643, H65664, T62713, 45 H16554, N21122, AA351037, AA484621, AA221492, AA259314, C76383, C76336, AA607924, C76394, AA408562, AA921258, AI006352, W41405, AA153317, AA015435, AA027405, AA794066, AA498038, AA184222, AI011068, AA859614, AA899776, AA955080, AA799674, AA849652, AI009788, AA900928, AI007950, AA109392, AA753592, U92780, AA957632, AA567950, AI009495.

## SEQ ID NO. 14:

5 AC000075, U66140, R14195, AA220229, T31199, R19104, R19148, Z46126, AA417619, Z45284, H14105, R84666, AA090321, AA350108, W52840, R48497, R13097, T66255, W44467, AA247676, AA198489, AA388175, AA261453, AA237111, AA790730, AA162394, AA816498, AI013729, AA684961, AA979759.

## 10 SEQ ID NO. 15:

AF069301, D10651, U11419, U11287, M91562, U90278, U72724, X57855, X79424, M16512, M64542, Z14152, AF016667, L01488, Z75955, AF024504, M13968, W67775, AA934587, AA617696, AA913577, AA628682, W74527, AA969876, AA995606, AA622402, AA027090, 15 AA620556, AA085733, AA187157, AI031865, AA972318, AA897169, W79046, AA531124, AA733183, T90909, Z25096, AA721771, AA115089, T49643, R00622, N93780, R00626, AA365494, T71475, N74066, AA027130, T83325, AA115569, AA658299, T55344, T83700, AA426250, AA393863, AA282967, R08138, AI000112, AA807574, AA077926, AA397527, W87761, AA243026, R56368, H16371, AA958697, AA003997, AA008542, AA036229, 20 AA397074, AA250467, AA260498, AA968175, AA253686, AA727785, AI019478, AA474978, AA543461, AA990281, AA245791, AA617042, AA015355, AA983015, AA982200, AA120064, AA462778, AA242574, AA986993, AA986911, AA882490, AA223057, AA543989, W65528, AA848318, AA874979, AA800547, AA945302, AA140994, AA991110, AA851120.

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## SEQ ID NO. 16:

Z68106, X14199, M14872, Z63497, M31670, AC002123, Z63498, AA280070, AA215687, H93207, AA070367, W95534, AA682436, AA741066, AA173269, AA641255, AA215688, 30 AA724798, N23259, AA442155, AA634563, AA074699, AA642322, AA861347, AA283655, AI002587, W95419, AA357042, AA761253, AA197191, T54480, AA133029, AA378991, AA114599, AA219925, AA174327, AA003800, C86661, AA990433, AA277014, AA445101, AA671205, AI036728, AA241221, AA213304, AI035350, W08919, W36663, AA061406, 35 AA144736, AA240583, AI006563, AA980152, AA250075, AA088967, W17488, AA098269, W10200, AA543712, AA755434, AI012680, AA820868, AA949519, AA391130, AA202576, AA979150, AA012391, AA539472.

## 40 SEQ ID NO. 17:

J03592, M24103, AB009386, U44832, J02966, M24102, U27316, U10404, X70847, D12771, D12770, J02683, J03591, U27315, M76669, U39779, M13783, J04982, X74510, X61667, M57424, L78810, AC004000, Z75206, U68723, Z75207, AF009661, X53264, J03320, U66060, 45 AB011800, M77194, AE000021, L07268, AE000936, U03115, AF009663, AA582128, AA916851, AA576667, AA915921, AA916853, N58735, AA428106, AA427849, AI024255, H69807, H11315, N36980, H69597, AA826334, W05080, N37044, AA385873, N48222, AA394173, AA837522, AI002511, AA292870, T96300, AA360716, AA379604, AA862844, AA430455, AA479859, AA133899, AA669954, H92542, AA095298, AA995794, AI003667.

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## SEQ ID NO. 18:

35 U14003, AE000500, X66784, AF030178, U77066, M10122, M69106, X58072, Z99113, AF004104, AF004101, X55037, X78560, AC004595, X55122, AA481578, AA280143, AA481271, AA280144, AA736516, N79995, R82883, AA355987, AA571000, AA572293, AA738653, AA620225, AA855746, AA563168, AA530645, W40812, AA690944, AA839456, X61848, AA525648, AA141861, AA944854, C94212, AA394778, C83861, H76642, 40 AA559379, AA943112.

## SEQ ID NO. 19:

45 AE000500, AF030178, X66784, Z49405, M69106, M27174, X55037, AF004104, X78560, U51281, L17405, M10122, AC003106, X55122, X05553, AC002368, AF004101, U77066, U77456, X58072, AA481578, AA280143, AA481271, AA280144, AA736516, AA780050, AA359089, R82883, AA355987, AA571000, AA563168, AA738653, AA620225, AA855746, AA572293, AA530645, W40812, AA690944, AA839456, X61848, AA525648, AA944854.

AA141861, C83861, AA943112, AA957703, H76642, C94212, AA394778.

## SEQ ID NO. 20:

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Z99496, AC004518, AC004219, Z70204, J03925, Z66494, AC003053, U40072, AC002980, S52165, AB009051, M81884, AL021767, Z68164, M18044, J04145, AA383216, AA928132, Z19212, R84841, H83829, T71075, AA723804, H95329, AJ003438, W13441, AA199243, AA242009, AA272568, AA009230, AA880181, AA265864, AA124746, AA801108, AA874804.

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## SEQ ID NO. 21:

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U20864, AL021246, AA430998, AA050776, AA104086, AA414390, AA920944, AA624117, AA788028, H36635.

## SEQ ID NO. 22:

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Z81462, AF029308, AC004069, AL010265, AL023828, AC004026, AF076274, U96110, Z71181, AF000265, U59919, Z80108, X66974, Y15994, D50366, D50367, AA034417, AA053882, AA883340, AA132258, AA770253, AA132362, AA132257, T62545, AA425357, AA721474, AA483037, AA724043, AA491390, W27229, AA047351, AA247867, C01523, AA548452, AA024660, R53754, AA795672, AA199329, AA986113, C81340, AA914941, AA536730, AA819693, Z28994, AA142165, AA585560, Z26382.

25

## SEQ ID NO. 23:

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X60469, AC000394, L08048, X12597, D63874, U51677, S71186, D43920, U59897, AF026132, AB012725, L02751, D88509, M15825, AF017349, AB002361, L49022, Z82196, S68108, AC005266, M60450, M55514, AC004406, AF019611, AC000398, U28932, AF049850, X58671, AC004101, AC004687, AF062921, AF004294, M33190, M73049, U00665, L04132, AF039845, L06147, M60052, X56007, Y00500, X77934, U26708, AL022333, AL021710, AF005720, Y13901, AC003952, U02506, U61387, AC004491, M81784, U00763, M80414, U84223, X87461, AF006040, U82468, AF005900, U29175, D26156, L13025, AL021127, X87329, Z82076, U25126, M30298, M34041, S80994, L13856, J03806, U23805, U20951, D82352, M38742, U05192, D76432, M21683, U19460, L48363, D78647, U26259, M55017, L06098, L19713, U88047, S67316, U47276, U28389, U18650, M85183, U07886, U00762, X54504, S67319, M89788, AC002995, AC000370, D84418, Z46757, AA167070, AA595202, AA166712, C05079, AA632468, T64162, H14432, AA095130, AA304799, AA541691, W38700, AA593710, AA889358, AA079129, T64291, AA143566, AA481443, AA991543, AA404267, H92212, AA134178, AA991539, AA991535, AA134179, AA248062, AA079130, AA634670, D25983, H63841, AI025061, AA531274, AA366296, AA360842, F22618, AA366810, N88386, AA715713, T90564, N38949, AA045606, W07682, D55472, AA557452, AA600212, H89557, AA327933, D20752, AA083771, AA101746, AA563764, AA330028, AA987424, AA054783, D83849, R34185, D52874, R81133, D55190, AI034040, N26696, AA196344, AI041775, AA054719, M79245, H54611, AA813685, R43019, AA426205.

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AA527046, R10011, R14525, AA053848, H85928, N85207, AA536117, AA497040,  
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## SEQ ID NO. 24:

30 Z93928, U13881, U70475, X89811, X81456, U20532, X04724, J00748, M25585, J04807,  
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AA709564, AA688482, AA709549, AA286083, AA637633, AA863920, C86279, AA940262,  
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40 AA498683, AI046409, C85159, Z84147, AA893230, C06683, C06682, C06639, C06625,  
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SEQ ID NO. 25:

AF019412, AC004404, X06166, M65066, AF006040, R13835, Z43662, F07559, R87914,  
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10 AA734717, C72433, AA940925, T26042, AA998047, AA651398, AA712850, AA979380,  
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SEQ ID NO. 26:

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SEQ ID NO. 27:

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30 AA497692, AA855719, C85235, AA407160, AA516930, AA240636, W41595, AA475660,  
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35 SEQ ID NO. 28:

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5 SEQ ID NO. 29:

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SEQ ID NO. 30:

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SEQ ID NO. 31:

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SEQ ID NO. 32:

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30 N75780, C18589, AA083604, AA471140, AA354268, C06018, Z21605, L48853, H90908,  
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## SEQ ID NO. 33:

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U10079, U22176, Z97192, X86553, D16432, Z68908, X98417, X97752, AC005176, AC004235, AA211771, AA019927, AA621920, R49915, AA436746, D81089, F07201, AA279576, R61642, AA363761, N90952, AA351423, W85802, AA827923, N41673, AA452942, AA252094, W95240, AA188552, T99151, T53177, AA223851, AA677535,  
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## 20 SEQ ID NO. 34:

AF041845, U48436, AF012624, L76569, AF025020, AF060179, U51281, Z37092, L12249, D83476, AF017434, AF062008, Z97198, AP000046, AA367417, AA852175, W67669, AA303139, AA243251, AA896193, AA881167, AA989888, AA683969, W62376, AA250652,  
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## SEQ ID NO. 35:

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AF069301, D17030, D17201, S80107, M15888, U09205, J00127, J00128, M64982, L11356, M58569, AE001140, D10667, M77812, AF001548, U39850, AA188052, W28824, AA380387, AA393863, AA426250, F00243, AA157205, R00525, AA137720, AA244463, AA118832, W97106, AA674322, AA645183, AI020701, AI019310, AA717623, W48327, AA153061,  
35 AA103723, AA800548, T46478, AA751512, C10724, C60506, AA819627.

## SEQ ID NO. 36:

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U81160, U35246, U66865, AF036234, Z71178, R52780, AA336715, AA337057, R12336, AA296712, AA291962, AA336501, AA387806, AI020063, AA109010, AA867718, AA606883, C11880, AA698152, D65730, AA851373, AI028830, AA941242.

## 45 SEQ ID NO. 37:

## SEQ ID NO. 38:

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## SEQ ID NO. 39:

15 L41560, Z66499, AC003970, AE001177, AF051320, K02212, D88539, U35665, L41069,  
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## SEQ ID NO. 40:

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## SEQ ID NO. 89:

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SEQ ID NO. 91:

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## SEQ ID NO. 111:

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## SEQ ID NO. 113:

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SEQ ID NO. 115:

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SEQ ID NO. 117:

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SEQ ID NO. 119:

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SEQ ID NO. 121:

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SEQ ID NO. 123:

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SEQ ID NO. 125:

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SEQ ID NO. 127:

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SEQ ID NO. 129:

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SEQ ID NO. 131:

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SEQ ID NO. 135:

AC005175, L12168, M98474, U94696, M88485, Z95972, Z81557, S54909, U59831, 20 AB002387, U59832, AC004221, AC003993, AA505656, AI004052, AA975150, AA904315, R39951, AA908198, AA348001, AA348002, R39437, R39435, D21034, AA365146, AA813999, F12674, AA226122, T50818, AA143492, AA337395, AA003016, AA475640, W78672, AA517530, W45934, AA915424, W54264, AA168145, W11712, D34652, U92753, Z84127, U92730, AA438286, AA978864, AA941236, F14527, D47303, D15953, AA202003, 25 AA979012, AA440964, AA736036, AA246888, AA940864.

SEQ ID NO. 137:

30 AF064604, L63543, AE000647, AF064804, AA443401, AA334624, H69413, H69440, H69851, AA167818, AA830102, N64831, AA947764, AA453748, AA453830, R52194, T30970, AA903211, T32140, T30969, W05727, AA024651, C18655, AA386236, T69012, AA442992, AA452775, AA292522, AA223531, AA221067, AA004165, AA538370, AA067626, AA104327, AA874150, AA450950, AA692789, AA798137, AA119093, AA240418, 35 AA542585, AA520648, AA519835, AI045289, AA520246, AA849945, T75681, AA520090, AA651385, Z25578, AA585901, AA395446, C90090, AA713116, AA851675.

SEQ ID NO. 139:

40 M24603, X02596, Y00661, M15025, X06418, U07000, X52829, M19730, M30829, X52831, M30832, X14676, X52828, X52830, S72479, L02935, M64437, M17542, L19704, U01147, X07537, X14677, X14675, M17541, M17543, M19695, X76485, AF023460, X89600, U19759, AF039083, X71790, AC004679, AC002076, AF035456, M99565, Z72005, Z79997, AL021154, 45 Z98259, AC003108, L13706, AF018254, M69197, U67228, Z75887, U14661, M84472, AC005200, AC001228, AC004761, Z95124, AC002540, Z79699, AE000926, U43572, U51281, D82351, AB013379, U34879, AC002425, AC004598, AA338585, AA333142, AA126116, H55543, H55721, R54267, H55614, H55699, H55545, AA744741, AA772917, H29052, AA573543, T16608, AA773472, AA775416, AA601919, AA470534, AA351521.

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SEQ ID NO. 141:

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20

SEQ ID NO. 143:

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SEQ ID NO. 145:

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45 SEQ ID NO. 147:

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SEQ ID NO. 149:

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5 AA732931, AA610556, AA973899, AA598896, AA531553, AA826535, AI000209, AA290836,  
AA642711, AA085920, W22275, D20744, UMGS017, AA487868, AA487869, AA085919, 682  
AA833281, AA619252, C77541, AA691960, AA763615, AA164051, AA259589, AA060475,  
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10  
SEQ ID NO. 151:

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L12399.

15  
SEQ ID NO. 153:

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20  
SEQ ID NO. 155:

25 X54859, Z86000, AC003043, X77738, X77737, L35930, AC003084, AC000111, M89651,  
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30 AA904521, AA372550, R48898, N50390, R08712, H83343, AA417867, AA090407,  
AA009846, AA927286, AA678135, AI033148, AI041408, AA235113, AA398662, M62215,  
W27276, AA885767, AA460155, AA742433, R19908, AA040696, AA555240, AA043160,  
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AI046716, AA237153, W15784, AA547132, AA231089, AA170968, D46090, C61892,  
35 C64408, D34777, D35175, D35914, D37381, AA559708, D37143, C60784, AI008855,  
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40  
SEQ ID NO. 157:

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45  
SEQ ID NO. 159:

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## SEQ ID NO. 161:

5 K01546, AE000468, X95549, AC004014, Z81584, L19201, X94244, X06932, U39479, X13301, AC000386, U80847, X86737, U39478, AA883211, AA610050, AA774254, AA280736, AA926725, AA459300, N55370, AA233666, H90342, T66839, H91250, AA856968, R92873, AI034196, AI014787, AA910410, AA088535, AA230765, AA467238,  
10 AA397279, AA420226, AA396042, AA200070, AA165873, AA762534, AA067133, AA065429, AA185092, AA572057, AA111387, AA175824, AA881071, AA571692, AA104279, AA733670, AI008804, D86670, C67200, D41938, AA141467, D35894, AI001643, AA957220, T37355, T18792, D47809, W21723, AA898504, AA951903, AA661025, AA949796, AA990685, AA661449, AA948837, R04787, D16046, AA439636, AA246769,  
15 AA978829, D43523, T02021, AA803212, D22651, AA201227, AA694728, AA891643, D23309, AA820831, D41871, W21774, D16065.

## SEQ ID NO. 163:

20 X15183, AF028832, D87666, J04633, L33676, X07270, U94395, M27024, M30627, X16857, X07265, M36830, M30626, AA669137, AA725103, AA890496, AA314095, AA554815, AA313331, AA730100, AA214035, AA876412, AA121630, AA314010, AA927532, AA968674, AA679253, N66271, AA558907, AA309988, AA587079, AA075436, AA160964,  
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30 AA657352, AA522607, AA188113, AA026444, AI003623, AA312717, AA312400, T64299, AA178992, AA228992, AI042136, AA457613, AI032857, AA164461, AA625127, AA807763, AA130815, AA054695, AA937097, W93534, N67875, AA526896, W52802, AA527942, N34251, W28646, AA668543, AA496091, W52511, AA070581, AA306826, AA120908, AA699607, AA086423, N72134, AA630369, AA564649, AA046806, AA666249, AA306893,  
35 AA225404, AA127417, AA854951.

## SEQ ID NO. 165:

40 M23885, AF047868, AF017732, AB005249, Z83229, AF026483, U97194, Z67884, Z67881, X13481, X07651, AC001226, AC002542, AB002307, AA984684, AA017533, AA306600, AA261957, F08123, R17885, AA282208, H85861, H85836, AA593150, H87276, AA057384, AA243602, AA013399, AA374926, AA721341, R88896, AA021538, AA101740, AA375314, AA090398, H86058, AA984556, AA215816, AA092672, AA034243, AA328017, F11174,  
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AA239037, AA672620, AA915168, AA863498, AA123378.

SEQ ID NO. 167:

5

Y11251, AF030234, AF043945, L40407.

SEQ ID NO. 169:

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U33822, X61838, AA572230, AA589570, AA929790, AA104830, C81582, AA271190, AA290278, AA543616, AI043207, AA107832, AA958460, AI020992, AA795905, AA277468, AA475069, AA111610, AA389139, AA154163.

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SEQ ID NO. 170:

D32050, D16969, AC004423, S81497.

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SEQ ID NO. 172:

D86982, L07131, M14544, AA296228, AA318436, AA296234, H88394, W26642, AF038251, AA394101, N35855, N56791, N35444, AA147382, AA647547, AA939939, AA895989, 25 AA122437, AA277698, W75741, AI036117, AA980469, AA033178, AI006694, AA980625, AA033190, AA175922, AA172918, AA895209, AA028700, AA416048, AA175247, AA217057, AI045760, R64866, D40836, D41873, AA509279, D40089, AA114361, AA751642, AA848690, AA800525, AA802510, C24001, AA841755, AA882663, D40069, AA433358, D40199, AA958134, AA072494, AI008727, AA618978, AA848687, C21884, AA113662, 30 AA945653, AA660093, C58446, AA908068, AA532100, AA264560, AA426658, AA097169, AA751535.

SEQ ID NO. 174:

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Z81364, AC003033, AE000665, AA570483, AA532739, AA526905, AA725306, AA134415, AA651838, AA481316, AA600310, C04532, AA004615, H20713, AA913640.

40 \_SEQ ID NO: 176

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45 SEQ ID NO: 198

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5 SEQ ID NO: 263

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SEQ ID NO:264

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35 SEQ ID NO:265

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15 SEQ ID NO: 270

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SEQ ID NO: 271

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## SEQ ID NO: 275

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25 SEQ ID NO: 319

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35 SEQ ID NO: 320

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5 SEQ ID NO: 321

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45 SEQ ID NO: 328



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35 SEQ ID NO.336

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## 30 SEQ ID NO.339

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## SEQ ID NO.340

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SEQ ID NO: 486

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10 SEQ ID NO: 490

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25 SEQ ID NO: 491

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## SEQ ID NO: 504

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10 SEQ ID NO: 506

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20 SEQ ID NO: 507

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35 SEQ ID NO: 508

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45 SEQ ID NO: 514

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5 SEQ ID NO: 519

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25 SEQ ID NO:599

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 AA975130, AA975130 on06f01.s1 NCI\_CGAP\_Lei2 Homo sapiens cDNA... 579 e-163  
 AA885226, AA885226 am34e06.s1 Soares NFL T GBC S1 Homo sapien... 559 e-157  
 AA912472, AA912472 ol96e03.s1 NCI\_CGAP\_PNS1 Homo sapiens cDNA... 555 e-156  
 AA320935, AA320935 EST23388 Adipose tissue, white II Homo sap... 553 e-155

AA042872, AA042872 zk56b07.s1 Soares pregnant uterus NbHPU Ho... 543 e-152  
 T08932, T08932 EST06824 Homo sapiens cDNA clone HIBBM46 5' end. 537 e-150  
 AA488258, AA488258 ad08f07.r1 Soares NbHFB Homo sapiens cDNA ... 533 e-149  
 T19350, T19350 h03012t Testis 1 Homo sapiens cDNA clone h0301... 496 e-138  
 H87681, H87681 yw15e04.r1 Homo sapiens cDNA clone 252318 5'. 490 e-136  
 H81522, H81522 yu61h08.r1 Homo sapiens cDNA clone 230655 5'. 466 e-129  
 T49620, T49620 ya77g03.s1 Homo sapiens cDNA clone 67732 3'. 452 e-125  
 R14363, R14363 yf80d10.r1 Homo sapiens cDNA clone 28995 5' si... 446 e-123  
 AA211476, AA211476 zp75h11.s1 Stratagene HeLa cell s3 937216 ... 430 e-118  
 N46636, N46636 yy48a09.r1 Homo sapiens cDNA clone 276760 5'. 424 e-116  
 Z17358, HSDHII065 H. sapiens partial cDNA sequence; clone HI... 416 e-114  
 R40737, R40737 yf80d10.s1 Homo sapiens cDNA clone 28995 3'. 400 e-109  
 AA410278, AA410278 zv32f05.r1 Soares ovary tumor NbHOT Homo s... 383 e-104  
 AA496574, AA496574 zv37b03.s1 Soares ovary tumor NbHOT Homo s... 375 e-101  
 N34907, N34907 yy48a09.s1 Homo sapiens cDNA clone 276760 3'. 371 e-100  
 T49619, T49619 ya77g03.r1 Homo sapiens cDNA clone 67732 5'. 355 1e-95  
 AA301480, AA301480 EST14551 Thymus III Homo sapiens cDNA 5' end 341 2e-91  
 R31593, R31593 yh76f03.s1 Homo sapiens cDNA clone 135677 3'. 317 2e-84  
 AA984591, AA984591 am89d10.s1 Stratagene schizo brain S11 Hom... 313 4e-83  
 AA338831, AA338831 EST43831 Fetal brain I Homo sapiens cDNA 5... 238 2e-60  
 T07305, T07305 EST05194 Homo sapiens cDNA clone HFBEG86. 230 4e-58  
 AA159942, AA159942 zo79c05.r1 Stratagene pancreas (#937208) H... 204 3e-50  
 R57355, R57355 F2878 Fetal heart Homo sapiens cDNA clone F287... 196 6e-48  
 AA729237, AA729237 nx35c08.s1 NCI\_CGAP\_GC4 Homo sapiens cDNA ... 192 1e-46  
 AA877709, AA877709 nr09g11.s1 NCI\_CGAP\_Co10 Homo sapiens cDNA... 172 9e-41  
 AA969195, AA969195 op51c03.s1 Soares\_NFL\_T\_GBC\_S1 Homo sapien... 107 4e-21  
 AA327432, AA327432 EST30768 Colon I Homo sapiens cDNA 5' end 80 1e-12  
 AA854147, AA854147 aj71f01.s1 Soares parathyroid tumor NbHPA ... 74 6e-11  
 AA983156, AA983156 oq51g09.s1 NCI\_CGAP\_Kid5 Homo sapiens cDNA... 66 2e-08  
 H09529, H09529 yl95h10.s1 Homo sapiens cDNA clone 46129 3'. 66 2e-08  
 AA286791, AA286791 zs54h07.r1 NCI\_CGAP\_GCB1 Homo sapiens cDNA... 66 2e-08  
 W04418, W04418 za43c06.r1 Soares fetal liver spleen 1NFLS Hom... 58 4e-06  
 AA101045, AA101045 zm27e12.r1 Stratagene pancreas (#937208) H... 56 1e-05  
 AA064706, AA064706 zm13f07.r1 Stratagene pancreas (#937208) H... 42 0.22  
 AA810035, AA810035 od11f12.s1 NCI\_CGAP\_GCB1 Homo sapiens cDNA... 40 0.86  
 T41169, T41169 ya31g10.s3 Homo sapiens cDNA clone 62274 3' co... 40 0.86  
 AA070108, AA070108 zm69d06.s1 Stratagene neuroepithelium (#93... 40 0.86  
 AA706183, AA706183 ag93e01.s1 Stratagene hNT neuron (#937233)... 40 0.86  
 AA393069, AA393069 zt69e09.r1 Soares testis NHIT Homo sapiens ... 40 0.86  
 AA371600, AA371600 EST83650 Pituitary gland, subtracted (prol... 40 0.86  
 AA977820, AA977820 oq78a09.s1 NCI\_CGAP\_Kid6 Homo sapiens cDNA... 38 3.4  
 AA584760, AA584760 no04c06.s1 NCI\_CGAP\_Phe1 Homo sapiens cDNA... 38 3.4  
 AA584615, AA584615 no08g12.s1 NCI\_CGAP\_Phe1 Homo sapiens cDNA... 38 3.4  
 AA229827, AA229827 nc48c04.r1 NCI\_CGAP\_Pr3 Homo sapiens cDNA ... 38 3.4  
 W21398, W21398 zb50a11.r1 Soares fetal lung NbHL19W Homo sapi... 38 3.4

AA136933, AA136933 zn97f07.s1 Stratagene fetal retina 937202 ... 38 3.4

AA869501, AA869501 vq08g11.r1 Barstead stromal cell line MPLR... 833 0.0  
 AA221749, AA221749 my28g01.r1 Barstead mouse pooled organs MP... 789 0.0  
 AA271363, AA271363 va71d08.r1 Soares mouse 3NME12 5 Mus muscu... 781 0.0  
 AA544727, AA544727 vk35d01.r1 Soares mouse mammary gland NbMM... 773 0.0  
 W84968, W84968 mf42e02.r1 Soares mouse embryo NbME13.5 14.5 M... 640 0.0  
 AA153324, AA153324 ms61e11.r1 Stratagene mouse embryonic carc... 617 e-175  
 AA673899, AA673899 vo86g07.r1 Barstead mouse irradiated colon... 583 e-164  
 AA797488, AA797488 vw28a05.r1 Soares mouse mammary gland NbMM... 519 e-145  
 W71831, W71831 me45b06.r1 Soares mouse embryo NbME13.5 14.5 M... 472 e-131  
 AA213358, AA213358 mu74e04.r1 Stratagene mouse embryonic carc... 444 e-123  
 W75918, W75918 me82f05.r1 Soares mouse embryo NbME13.5 14.5 M... 444 e-123  
 AA038141, AA038141 mi81e05.r1 Soares mouse p3NMF19.5 Mus musc... 359 3e-97  
 AA038288, AA038288 mi83b04.r1 Soares mouse p3NMF19.5 Mus musc... 323 1e-86  
 AA017742, AA017742 mh40c03.r1 Soares mouse placenta 4NbMP13.5... 297 8e-79  
 AA771297, AA771297 vt17g04.r1 Barstead mouse myotubes MPLRB5 ... 297 8e-79  
 AA105228, AA105228 mp45b11.r1 Barstead MPLRB1 Mus musculus cD... 295 3e-78  
 AA068340, AA068340 mm53f01.r1 Stratagene mouse embryonic carc... 293 1e-77  
 AA612347, AA612347 vo05c08.r1 Stratagene mouse skin (#937313)... 281 5e-74  
 AA038300, AA038300 mi83d04.r1 Soares mouse p3NMF19.5 Mus musc... 270 2e-70  
 AA500952, AA500952 vg01h04.r1 Soares mouse NbMH Mus musculus ... 252 4e-65  
 W08368, W08368 mb41f07.r1 Soares mouse p3NMF19.5 Mus musculus... 212 4e-53  
 AA052280, AA052280 ma82e12.r1 Soares mouse p3NMF19.5 Mus musc... 123 3e-26  
 AA064466, AA064466 ml49c05.r1 Stratagene mouse testis (#93730... 107 2e-21  
 AA271566, AA271566 vb74b09.r1 Soares mouse 3NME12 5 Mus muscu... 60 3e-07  
 C86222, C86222 Mus musculus fertilized egg cDNA 3'-end seque... 42 0.078  
 W83632, W83632 mf31a04.r1 Soares mouse embryo NbME13.5 14.5 M... 42 0.078  
 AA423627, AA423627 ve80f01.r1 Soares mouse mammary gland NbMM... 42 0.078  
 AA036586, AA036586 mi41h08.r1 Soares mouse embryo NbME13.5 14... 42 0.078  
 AA207496, AA207496 mv78g02.r1 GuayWoodford Beier mouse kidney... 42 0.078  
 AA120433, AA120433 mp82h11.r1 Soares 2NbMT Mus musculus cDNA ... 42 0.078  
 W08185, W08185 mb42h02.r1 Soares mouse p3NMF19.5 Mus musculus... 38 1.2  
 AA065563, AA065563 ml71b06.r1 Stratagene mouse kidney (#93731... 38 1.2  
 AA288756, AA288756 mr46h07.r1 Life Tech mouse embryo 15 5dpc ... 38 1.2  
 AA119334, AA119334 mp80e10.r1 Soares 2NbMT Mus musculus cDNA ... 38 1.2  
 AA163051, AA163051 ms24a10.r1 Stratagene mouse skin (#937313)... 38 1.2  
 N28074, N28074 MDB1392R Mouse brain, Stratagene Mus musculus ... 38 1.2  
 AA288757, AA288757 mr46h08.r1 Life Tech mouse embryo 15 5dpc ... 38 1.2  
 AA122857, AA122857 mq06a02.r1 Soares 2NbMT Mus musculus cDNA ... 38 1.2  
 AA617519, AA617519 vj77d05.r1 Knowles Solter mouse blastocyst... 38 1.2

W89420, W89420 mf80b03.r1 Soares mouse embryo NbME13.5 14.5 M... 38 1.2  
AI047837, AI047837 ud64c11.x1 Sugano mouse liver mlia Mus mus... 38 1.2  
AA840310, AA840310 vw91a10.r1 Stratagene mouse skin (#937313)... 36 4.8  
AA986428, AA986428 ue13b04.x1 Sugano mouse embryo mewa Mus mu... 36 4.8  
W47677, W47677 mc89g07.r1 Soares mouse embryo NbME13.5 14.5 M... 36 4.8  
AA057996, AA057996 mj56c10.r1 Soares mouse embryo NbME13.5 14... 36 4.8  
AA183858, AA183858 mo95h01.r1 Stratagene mouse testis (#93730... 36 4.8  
AA212232, AA212232 mu43e08.r1 Soares 2NbMT Mus musculus cDNA ... 36 4.8  
W41067, W41067 mc39a06.r1 Soares mouse p3NMF19.5 Mus musculus... 36 4.8  
AA967594, AA967594 uh01d06.r1 Soares mouse hypothalamus NMHy ... 36 4.8  
AA414093, AA414093 vc64c07.s1 Knowles Solter mouse 2 cell Mus... 36 4.8  
AA123833, AA123833 mp93c03.r1 Soares 2NbMT Mus musculus cDNA ... 36 4.8  
AA432920, AA432920 vd91b11.r1 Soares mouse NbMH Mus musculus ... 36 4.8  
AA874496, AA874496 vx03a08.r1 Soares 2NbMT Mus musculus cDNA ... 36 4.8  
AA000433, AA000433 me76e09.r1 Soares mouse embryo NbME13.5 14... 36 4.8  
AA023983, AA023983 mh94a07.r1 Soares mouse placenta 4NbMP13.5... 36 4.8  
AA013726, AA013726 mh12e09.r1 Soares mouse placenta 4NbMP13.5... 36 4.8  
AA274648, AA274648 vb08c01.r1 Soares mouse NML Mus musculus c... 36 4.8  
AA140347, AA140347 mq89g06.r1 Stratagene mouse heart (#937316... 36 4.8  
AA499377, AA499377 vi89c07.r1 Stratagene mouse heart (#937316... 36 4.8  
C88747, C88747 Mus musculus early blastocyst cDNA, clone 01B... 36 4.8  
AA726125, AA726125 vu88c06.r1 Stratagene mouse skin (#937313)... 36 4.8  
AA760311, AA760311 vv71c12.r1 Stratagene mouse skin (#937313)... 36 4.8  
AA763007, AA763007 vw60b05.r1 Soares mouse mammary gland NMLM... 36 4.8  
AA929878, AA929878 vz44d03.r1 Soares 2NbMT Mus musculus cDNA ... 36 4.8  
W59064, W59064 md67e10.r1 Soares mouse embryo NbME13.5 14.5 M... 36 4.8  
AA103519, AA103519 mo24b12.r1 Life Tech mouse embryo 13 5dpc ... 36 4.8  
AA222310, AA222310 my14d08.r1 Barstead mouse heart MPLRB3 Mus... 36 4.8  
W83557, W83557 mf32d02.r1 Soares mouse embryo NbME13.5 14.5 M... 36 4.8  
AA168631, AA168631 ms33c05.r1 Stratagene mouse skin (#937313)... 36 4.8  
AA960143, AA960143 vw60b05.s1 Soares mouse mammary gland NMLM... 36 4.8  
W34557, W34557 mc58a05.r1 Soares mouse embryo NbME13.5 14.5 M... 36 4.8  
W98818, W98818 mf94e06.r1 Soares mouse embryo NbME13.5 14.5 M... 36 4.8  
AA008527, AA008527 mg85h01.r1 Soares mouse embryo NbME13.5 14... 36 4.8  
AA008734, AA008734 mg86h03.r1 Soares mouse embryo NbME13.5 14... 36 4.8  
AA510568, AA510568 vg33a10.r1 Soares mouse mammary gland NbMM... 36 4.8  
AA672524, AA672524 vo59e11.r1 Soares mouse mammary gland NbMM... 36 4.8  
AA052773, AA052773 mf24h01.r1 Soares mouse embryo NbME13.5 14... 36 4.8  
AA096626, AA096626 mo09h06.r1 Life Tech mouse embryo 10 5dpc ... 36 4.8  
AA124880, AA124880 mp73e06.r1 Soares 2NbMT Mus musculus cDNA ... 36 4.8  
AA198005, AA198005 mv12b09.r1 GuayWoodford Beier mouse kidney... 36 4.8  
AA624213, AA624213 vm98h06.r1 Knowles Solter mouse blastocyst... 36 4.8  
AA521863, AA521863 vi08b01.r1 Barstead mouse myotubes MPLRB5 ... 36 4.8  
AA692113, AA692113 vt19d03.r1 Barstead mouse myotubes MPLRB5 ... 36 4.8  
W71551, W71551 me39e11.r1 Soares mouse embryo NbME13.5 14.5 M... 36 4.8

AA646501, AA646501 vn12g12.r1 Stratagene mouse heart (#937316... 36 4.8  
 AA607056, AA607056 vm95e05.r1 Knowles Solter mouse blastocyst... 36 4.8  
 AA163340, AA163340 ms65b10.r1 Stratagene mouse embryonic carc... 36 4.8  
 AA110893, AA110893 mm02b04.r1 Stratagene mouse kidney (#93731... 36 4.8  
  
 AI030290, AI030290 UI-R-C0-jb-d-01-0-UI.s1 UI-R-C0 Rattus nor... 293 1e-77  
 C71833, C71833 Rice cDNA, partial sequence (E0428\_1A) 44 0.017  
 AA926551, AA926551 TENS1173 T. cruzi epimastigote normalized ... 42 0.069  
 AA875699, AA875699 TENU0170 T.cruzi epimastigote normalized c... 42 0.069  
 AA567661, AA567661 HL01595.5prime HL Drosophila melanogaster ... 40 0.27  
 C74504, C74504 Rice cDNA, partial sequence (E31753\_1A) 40 0.27  
 AA698333, AA698333 HL04291.5prime HL Drosophila melanogaster ... 38 1.1  
 AA441429, AA441429 LD16359.5prime LD Drosophila melanogaster ... 38 1.1  
 N68770, N68770 TgESTzy35b12.r1 TgRH Tachyzoite cDNA Toxoplasma... 38 1.1  
 AA246440, AA246440 LD05311.5prime LD Drosophila melanogaster ... 38 1.1  
 AA801776, AA801776 GM12975.5prime GM Drosophila melanogaster ... 38 1.1  
 N69148, N69148 TgESTzy33d10.r1 TgRH Tachyzoite cDNA Toxoplasma... 38 1.1  
 AA536484, AA536484 LD17114.5prime LD Drosophila melanogaster ... 38 1.1  
 AA392544, AA392544 LD11451.5prime LD Drosophila melanogaster ... 38 1.1  
 AA202696, AA202696 LD03182.5prime LD Drosophila melanogaster ... 38 1.1  
 AA392367, AA392367 LD11287.5prime LD Drosophila melanogaster ... 38 1.1  
 AA264629, AA264629 LD08245.5prime LD Drosophila melanogaster ... 38 1.1  
 AA735318, AA735318 LD21104.5prime LD Drosophila melanogaster ... 38 1.1  
 AA264558, AA264558 LD08333.5prime LD Drosophila melanogaster ... 38 1.1  
 AA536476, AA536476 LD17106.5prime LD Drosophila Embryo Drosop... 38 1.1  
 AA957774, AA957774 UI-R-E1-fv-f-04-0-UI.s1 UI-R-E1 Rattus nor... 38 1.1  
 AA567991, AA567991 HL02092.5prime HL Drosophila melanogaster ... 38 1.1  
 AA957876, AA957876 UI-R-E1-fv-f-04-0-UI.s2 UI-R-E1 Rattus nor... 38 1.1  
 AA892488, AA892488 EST196291 Normalized rat kidney, Bento Soa... 38 1.1  
 AA699001, AA699001 HL06668.5prime HL Drosophila melanogaster ... 36 4.3  
 C19706, C19706 Rice cDNA, partial sequence (E10809\_1A) 36 4.3  
 D41773, RICS4574A Rice cDNA, partial sequence (S4574\_2A). 36 4.3  
 C40680, C40680 C.elegans cDNA clone yk247c4 : 5' end, single... 36 4.3  
 AA698625, AA698625 HL05354.5prime HL Drosophila melanogaster ... 36 4.3  
 C82819, C82819 Oryctolagus cuniculus corneal endothelial cDN... 36 4.3  
 D46016, RICS10393A Rice cDNA, partial sequence (S10393\_3A). 36 4.3  
 AA536314, AA536314 LD16858.5prime LD Drosophila melanogaster ... 36 4.3  
 AA801012, AA801012 EST190509 Normalized rat muscle. Bento Soa... 36 4.3  
 D46541, RICS11289A Rice cDNA, partial sequence (S11289\_1A). 36 4.3  
 D47315, RICS12612A Rice cDNA, partial sequence (S12612\_1A). 36 4.3  
 AA735857, AA735857 GM09977.5prime GM Drosophila melanogaster ... 36 4.3  
 AA753921, AA753921 97BS0370 Rice Immature Seed Lambda ZAPII c... 36 4.3  
 D47243, RICS12505A Rice cDNA, partial sequence (S12505\_1A). 36 4.3  
 AA978395, AA978395 LD28411.5prime LD Drosophila melanogaster ... 36 4.3

D15134, RICC0136A Rice cDNA, partial sequence (C0136A). 36 4.3  
 D46483, RICS11185A Rice cDNA, partial sequence (S11185\_1A). 36 4.3  
 D46618, RICS11395A Rice cDNA, partial sequence (S11395\_1A). 36 4.3  
 D46659, RICS11457A Rice cDNA, partial sequence (S11457\_1A). 36 4.3  
 D46719, RICS11572A Rice cDNA, partial sequence (S11572\_1A). 36 4.3  
 D48579, RICS14880A Rice cDNA, partial sequence (S14880\_2A). 36 4.3  
 AA802334, AA802334 GM04219.5prime GM Drosophila melanogaster ... 36 4.3  
 D46066, RICS10470A Rice cDNA, partial sequence (S10470\_1A). 36 4.3  
 D47037, RICS12104A Rice cDNA, partial sequence (S12104\_1A). 36 4.3  
 D46874, RICS11807A Rice cDNA, partial sequence (S11807\_2A). 36 4.3  
 D47174, RICS12340A Rice cDNA, partial sequence (S12340\_2A). 36 4.3  
 T04578, T04578 625 Lambda-PRL2 Arabidopsis thaliana cDNA clon... 36 4.3  
 C83675, C83675 Oryctolagus cuniculus corneal endothelial cDN... 36 4.3  
 D47950, RICS13762A Rice cDNA, partial sequence (S13762\_1A). 36 4.3  
 R90044, R90044 16399 Lambda-PRL2 Arabidopsis thaliana cDNA cl... 36 4.3  
 D46994, RICS12013A Rice cDNA, partial sequence (S12013\_2A). 36 4.3  
 AA440820, AA440820 LD15713.5prime LD Drosophila melanogaster ... 36 4.3  
 C72089, C72089 Rice cDNA, partial sequence (E0963\_1A) 36 4.3  
 Z84004, SSZ84004 S.scrofa mRNA; expressed sequence tag (5'; ... 36 4.3  
 D47519, RICS13070A Rice cDNA, partial sequence (S13070\_1A). 36 4.3  
 C19735, C19735 Rice cDNA, partial sequence (E10858\_1A) 36 4.3  
 D47231, RICS12462A Rice cDNA, partial sequence (S12462\_1A). 36 4.3  
 D47147, RICS12293A Rice cDNA, partial sequence (S12293\_1A). 36 4.3  
 AA950198, AA950198 LD30147.5prime LD Drosophila melanogaster ... 36 4.3  
 Z47624, ATTS4480 A. thaliana transcribed sequence; clone TAI... 36 4.3  
 D45955, RICS10259A Rice cDNA, partial sequence (S10259\_1A). 36 4.3  
 D47137, RICS12280A Rice cDNA, partial sequence (S12280\_1A). 36 4.3  
 D69927, CELK093H2F C.elegans cDNA clone yk93h2 : 5' end, sin... 36 4.3  
 AA392275, AA392275 LD11117.5prime LD Drosophila melanogaster ... 36 4.3

SEQ ID NO:546

D87455, D87455 Human mRNA for KIAA0266 gene, complete cds 1164 0.0  
 Z99129, HS425C14 Human DNA sequence from clone 425C14 on chr... 42 0.20  
 D90900, D90900 Synechocystis sp. PCC6803 complete genome, 2/... 40 0.80  
 Z74281, SCYDL233W S.cerevisiae chromosome IV reading frame O... 38 3.1  
 AL021528, HS394P21 Homo sapiens DNA sequence from PAC 394P21... 38 3.1  
 Z49155, HSL83D3 Human DNA from cosmid L83d3, Huntington's Di... 38 3.1  
 U33761, HSU33761 Human cyclin A/CDK2-associated p45 (Skp2) mR... 38 3.1  
 AF052832, AF052832 Trypanosoma cruzi CL Brener cosmid 1b21 ch... 38 3.1  
 Z98600, SPAC20G4 S.pombe chromosome I cosmid c20G4 38 3.1

Y09438, SPHUSPLUS *S.pombe* hus1+ gene 38 3.1  
 D29951, MUSKIF Mouse mRNA for kinesin family protein KIF1a, ... 38 3.1

## HUMAN ESTs

AA151187, AA151187 zo03c11.r1 Stratagene colon (#937204) Homo... 694 0.0  
 AA824593, AA824593 oc83d10.s1 NCI\_CGAP\_GCB1 Homo sapiens cDNA... 670 0.0  
 AA954862, AA954862 op20c03.s1 NCI\_CGAP\_Co12 Homo sapiens cDNA... 581 e-164  
 T16360, T16360 NIB1193 Normalized infant brain, Bento Soares ... 517 e-145  
 R54592, R54592 yg81h10.s1 Homo sapiens cDNA clone 40102 3'. 511 e-143  
 AA373594, AA373594 EST85631 HSC172 cells I Homo sapiens cDNA ... 507 e-142  
 AA100660, AA100660 zl90a05.r1 Stratagene colon (#937204) Homo... 383 e-104  
 R42009, R42009 yg05b04.s1 Homo sapiens cDNA clone 31336 3'. 379 e-103  
 AA249614, AA249614 k3041.seq.F Human fetal heart, Lambda ZAP ... 252 5e-65  
 AA360633, AA360633 EST69800 T-cell lymphoma Homo sapiens cDNA... 182 4e-44  
 AA053498, AA053498 zl70b11.r1 Stratagene colon (#937204) Homo... 38 1.5  
 AA992442, AA992442 or85h03.s1 NCI\_CGAP\_Lu5 Homo sapiens cDNA ... 38 1.5

AA065677, AA065677 mm43c03.r1 Stratagene mouse melanoma (#937... 297 4e-79  
 AA529728, AA529728 vi38g12.r1 Beddington mouse embryonic regi... 42 0.035  
 W91608, W91608 MTA.D10.092.A MTA adult mouse thymus library M... 42 0.035  
 AA177186, AA177186 mt51a11.r1 Stratagene mouse embryonic carc... 42 0.035  
 AA048008, AA048008 mj26h10.r1 Soares mouse embryo NbME13.5 14... 36 2.2  
 AA637535, AA637535 vu10c02.r1 Barstead mouse myotubes MPLRB5 ... 36 2.2  
 AA726355, AA726355 vu90c09.r1 Stratagene mouse skin (#937313)... 36 2.2  
 AA404025, AA404025 va31c11.r1 GuayWoodford Beier mouse kidney... 36 2.2  
 AA060014, AA060014 ml34d07.r1 Stratagene mouse testis (#93730... 36 2.2  
 AA870617, AA870617 vq23h10.r1 Barstead stromal cell line MPLR... 36 2.2  
 AA414112, AA414112 vc64f08.s1 Knowles Solter mouse 2 cell Mus... 36 2.2  
 AA764250, AA764250 vv49e09.r1 Soares 2NbMT Mus musculus cDNA ... 36 2.2

H34350, H34350 EST111226 Rat PC-12 cells, NGF-treated (9 days... 36 1.9  
 C40718, C40718 *C.elegans* cDNA clone yk247f9 : 5' end, single... 36 1.9  
 AA817925, AA817925 UI-R-A0-af-g-04-0-UI.s1 UI-R-A0 Rattus nor... 36 1.9  
 AA955650, AA955650 UI-R-E1-fc-e-10-0-UI.s1 UI-R-E1 Rattus nor... 36 1.9

SEQ ID NO:547

U66201, MMU66201 Mus musculus fibroblast growth factor homolo... 42 0.35  
 U66197, HSU66197 Human fibroblast growth factor homologous fa... 42 0.35  
 AF020738, AF020738 Mus musculus fibroblast growth factor-rela... 42 0.35  
 U85773, HSU85773 Human phosphomannomutase (PMM2) mRNA, comple... 40 1.4  
 Z46966, MMIMOGN44 M.musculus mRNA for imogen 44. 40 1.4  
 AC004301, AC004301 Drosophila melanogaster DNA sequence (P1 D... 40 1.4  
 U86662, LEU86662 Lycopersicon esculentum VPS41 (tVPS41) mRNA.... 40 1.4

## HUMAN ESTs

W22160, W22160 63A6 Human retina cDNA Tsp509I-cleaved sublibr... 791 0.0  
 AA860926, AA860926 ak22d06.s1 Soares testis NHT Homo sapiens ... 650 0.0  
 AA348243, AA348243 EST54707 Hippocampus I Homo sapiens cDNA 5... 513 e-143  
 AA551799, AA551799 nk04a11.s1 NCI\_CGAP\_Co2 Homo sapiens cDNA ... 363 4e-98  
 AA327309, AA327309 EST30621 Colon I Homo sapiens cDNA 5' end 353 3e-95  
 AA344913, AA344913 EST50856 Gall bladder II Homo sapiens cDNA... 337 2e-90  
 AA121174, AA121174 zl88g08.s1 Stratagene colon (#937204) Homo... 317 2e-84  
 AA121198, AA121198 zl88g08.r1 Stratagene colon (#937204) Homo... 317 2e-84  
 AA001561, AA001561 ze46e07.s1 Soares retina N2b4HR Homo sapie... 42 0.17  
 AA888147, AA888147 04h11.s1 NCI\_CGAP\_Co10 Homo sapiens cDNA... 40 0.67  
 AA946650, AA946650 oq38h09.s1 NCI\_CGAP\_Kid5 Homo sapiens cDNA... 40 0.67  
 AA435587, AA435587 zi85d07.s1 Soares testis NHT Homo sapiens ... 40 0.67  
 AA806381, AA806381 oc22g05.s1 NCI\_CGAP\_GCB1 Homo sapiens cDNA... 40 0.67  
 AA577174, AA577174 nm86c11.s1 NCI\_CGAP\_Co9 Homo sapiens cDNA ... 40 0.67  
 AA215903, AA215903 hp0042.seq.F Fetal heart, Lambda ZAP Expre... 40 0.67  
 AA262229, AA262229 zs25b12.s1 NCI\_CGAP\_GCB1 Homo sapiens cDNA... 40 0.67  
 AA969632, AA969632 op38h05.s1 Soares\_NFL\_T\_GBC\_S1 Homo sapien... 40 0.67  
 N35888, N35888 yy28b05.s1 Homo sapiens cDNA clone 272529 3'. 40 0.67  
 AI005324, AI005324 ou13h07.x1 Soares\_NFL\_T\_GBC\_S1 Homo sapien... 40 0.67  
 AA172158, AA172158 zp29a01.s1 Stratagene neuroepithelium (#93... 40 0.67  
 AA860208, AA860208 ak48c10.s1 Soares testis NHT Homo sapiens ... 40 0.67  
 AA814296, AA814296 nz07d08.s1 NCI\_CGAP\_GCB1 Homo sapiens cDNA... 40 0.67  
 AA873216, AA873216 oh70f04.s1 NCI\_CGAP\_Kid5 Homo sapiens cDNA... 40 0.67  
 AA403143, AA403143 zv66d01.r1 Soares total fetus Nb2HF8 9w Ho... 40 0.67  
 W45005, W45005 zc05c12.r1 Soares parathyroid tumor NbHPA Homo... 40 0.67  
 W32428, W32428 zc05c12.s1 Soares parathyroid tumor NbHPA Homo... 40 0.67  
 AA974988, AA974988 on59b06.s1 Soares\_NFL\_T\_GBC\_S1 Homo sapien... 40 0.67  
 AA725024, AA725024 ah97h10.s1 Soares\_NFL T GBC S1 Homo sapien... 40 0.67  
 AA757360, AA757360 ah98a01.s1 Soares\_NFL T GBC S1 Homo sapien... 40 0.67  
 N72025, N72025 yz96g02.s1 Homo sapiens cDNA clone 290930 3'. 40 0.67  
 R02514, R02514 ye70b08.r1 Homo sapiens cDNA clone 123063 5'. 40 0.67  
 AA039536, AA039536 zk39h10.s1 Soares pregnant uterus NbHPU Ho... 40 0.67  
 AA877455, AA877455 ob33g01.s1 NCI\_CGAP\_Kid5 Homo sapiens cDNA... 40 0.67  
 AA041240, AA041240 zf07g05.r1 Soares fetal heart NbHH19W Homo... 40 0.67